New Amphiphilic Palladium-Phosphine Complexex Bound to Solid Supports: Preparation and Use for Palladium-Catalyzed Reactions in Aqueous Media

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CONTENTS

General Introduction

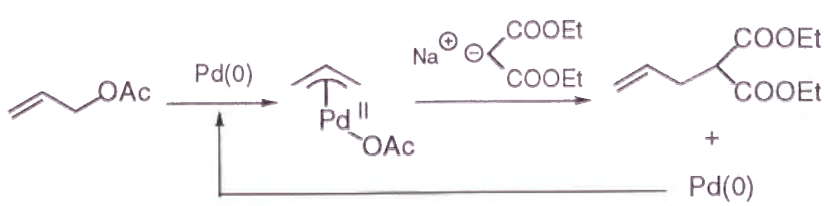
Owing to increasing environmental concerns about harmful and resource-consuming solvent waste,[1] the chemistry of organic transformations in water is presently undergoing very rapid growth.[2] On the other hand, development of immobilized reagents has been attracting significant interest for their practical advantages.[3] There is good reason to believe that immobilized catalysts exhibiting high catalytic activity in aqueous media offer a viable clean alternative to more traditional methods of accomplishing many organic reactions.[4,5,6] From these viewpoints, the author has focused his effort on developing the amphiphilic polymer-supported transition metal complexes which are of great interest because not only of their properties as heterogeneous catalyst but also of their catalytic activity in water. In particular, the reaction catalyzed by palladium–phosphine complex is thought to be one of the representatives and was mentioned herein this thesis.

Palladium-Catalyzed Reactions

Palladium-catalyzed reaction has proven to be one of the most powerful methods for organic transformation. A various types of palladium-catalyzed reactions, e.g., oxidation, reduction, carbon-carbon bond formation, etc., have been developed so far. In particular, a great deal of attention has been paid to allylic substitution reaction and cross-coupling reaction owing to their synthetic utility.

Allylic substitution reaction: Development of the palladium-catalyzed allylic substitution owes much to the works by Trost[7] and Tsuji,[8] who heightened this reaction to one of the most useful synthetic methods in organic synthesis using organometallic compounds. Many kinds of allylic esters are employed in this reaction. The reactivity of these allylic compounds are very different, and allylic acetates are widely used. Nucleophiles are also variegated; 1,3-dicarbonyl compounds such as malonate and β–keto esters, hydride, organometals such as Grignard and organozinc reagent, heteroatoms such as oxygen, nitrogen, phosphorus, sulfur, silicon, and tin nucleophiles. It has been

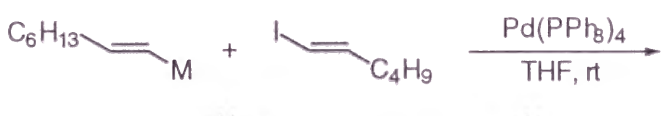
Scheme 1



well-investigated that the allylic substitution of allylic acetates takes place by way of π-allylpalladium(II) intermediates generated by oxidative addition of allylic acetates to palladium(0) species. The π-allylpalladiun complexes react with soft or hard nucleophiles to give the allylic substitution products and palladium(0). The reaction of allyl acetate with sodium salt of malonate shown in Scheme 1 is one of the representatives.

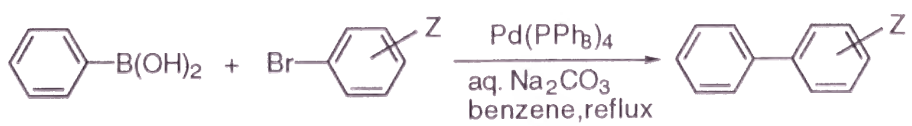
Cross-coupling reaction: In 1972, Tamao[9] and Corriu[10] reported independently that the reaction of organomagnesium reagents with alkenyl or aryl halides could be markedly catalyzed by Ni(II) complex. Kochi[11] found the efficiency of Fe(III) catalyst for the cross-coupling of Grignard reagents with 1-halo-1-alkenes and Li_2CuCl_4 catalyst for haloalkanes. The palladium-catalyzed reaction of Grignard reagents was first reported by Murahashi,[12] the synthetic utility of which was then amply demonstrated by Negishi[13] on the reactions of organoaluminum, zinc, and zirconium reagents (Scheme 2). Many other organometallic reagents have proven to be highly useful as nucleophiles for the cross-coupling reaction, e.g., organolithiums by Murahashi,[14] organostannans by Migita[15] and Stille,[16] 1-alkenylcopper(I) by Normant,[17] organosilicon compounds by Hiyama,[18] and organoborons by Suzuki and Miyaura.[19] Among the various systems, the combination of palladium catalyst and organoboron reagents, so-called Suzuki-Miyaura Coupling, has recognized as one of the most useful systems for catalytic cross-coupling reactions (Scheme 3).

Scheme 2



M = ZnCl	95	3	3
MgCl	32	7	8
Al(i-Bu)$_2$	75	7	6
Cp_2ZrCl	93	trace	trace
B(Sia)$_2$ (+ base)	65	5	1

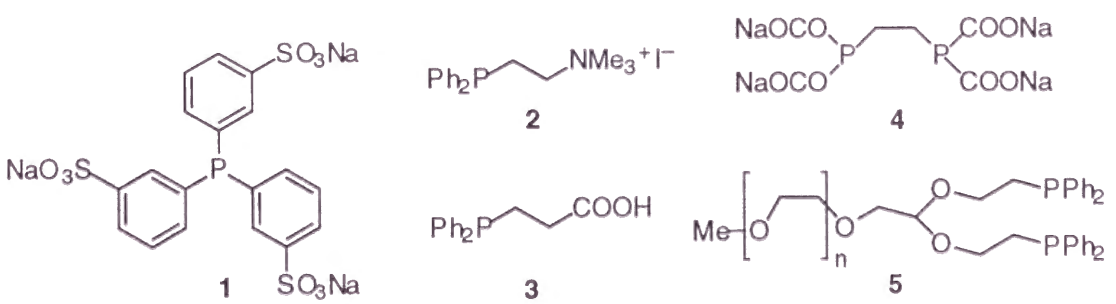
Scheme 3



Transition Metal-Catalyzed Reaction in Water

To achieve transition metal-catalyzed reactions in aqueous media, many classes of water-soluble phosphine ligands including sulfonate, ammonium, carboxylate, phosphonium, and hydroxyl group were prepared (Figure 1).[20] Owing to their diverse coordination chemistry, sulfonated phosphines such as TPPTS (**1**) is well-documented and used in a rhodium-catalyst for the production of butyraldehyde on an industrial scale.[21] Water-soluble phosphines can also result from the quaternization of the nitrogen atom of aminoalkyl and aminoaryl phosphines. The most important example of this class of substances is "amphos" (**2**), first synthesized by Baird.[22] Phosphines with carboxylic groups were some of the earliest investigated water-soluble phosphines. The first example **3** was prepared by Mann[23] in 1952 through cyanoethylation of diphenylphosphine with subsequent nitrile saponification. The development of the "carboxyalkylphosphines" (phosphinocarboxylic acid) was carried out predominantly by the research groups of Rauhut, Issleib, and Podlahová.[24] The most important example is the phosphine analog of ethylenediaminetetraacetic acid (**4**).[25] The phosphines substituted by polyether chain were also prepared.[26] Investigations into water-soluble hydroxyalkyl-substituted phosphines were carried out by Chatt in 1973.,[27] The phosphines are significantly soluble in water only if they carry several hydroxyalkyl groups.[28] The commercially available trisubstituted phosphine **5** is being tested in the form of metal complexes for catalytic propertied in the addition of PH_3 to formaldehyde.[29] Nickel, platinum, and palladium complexes of **5** were synthesized, and the elucidation of the structure of the palladium complex[$Pd\{P(CH_2OH)_3\}_4 \cdot CH_3OH$] was carried out by single crystal X-ray structural analysis.[30]

Figure 1

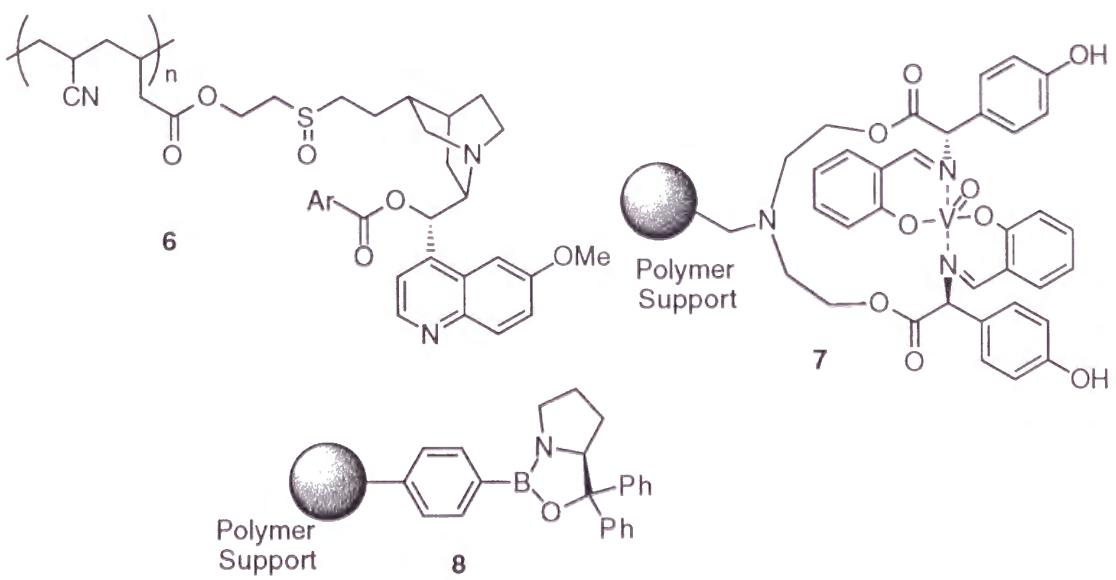


Polymer-Supported Catalyst

During the past two decades, intensive efforts have been devoted to develop solid-supported reagents.[3] Solid-supported catalysts introduce the advantages of

heterogeneous catalysts, such as easy separation from the products and facile recovery for recycling. Immobilization of catalysts on polymer-supports often causes significant decrease of catalytic activity or selectivity of the reactions due to the slower diffusion of substrates in the polymer matrix. Further decrease of catalytic activity or selectivity is expected to arise from utilizing a high degree of cross-linking of the polymer-support, although it is desirable to facilitate the treatments. As high-throughput synthesis by solution-phase chemistry is going in popularity with the advent of efficient methods for product purification, the development of solid-supported reagents, in particular catalysts, become progressively important. On the other hand, catalytic asymmetric reaction using an immobilized chiral catalyst has been recognized as an important goal in synthetic organic chemistry. The recent application of polymer-supported chiral catalysts have been reported by Sharpless[31] who was able to oxidize *trans*-stilbene in 81-87% yield and with 85-93% enantiomeric excess using the polymer-supported catalyst **76** (Figure 2), OsO_4 and *N*-methylmorpholine *N*-oxide (NMO). The yield were high but enantiomeric excesses were inferior to the corresponding homogeneous reactions. Several other catalysts have been studied.[32] Kumar have developed a polystyrene-based vanadiuml complex **80**, generated from diethanolamine, L-tyrosine, salicyl aldehyde and $VO(acac)_2$, to perform hydroxylations of benzene using 1 mol % of **80** and 1 equiv of H_2O_2.[50] After stirring at 65 °C for 6 h, a conversion of 30% was detected. The phenol could be easily separated from unreacted benzene by distillation. A polymer-bound oxazaborolidine[32a] was developed and successfully used in the asymmetric reduction of acetophenone to give 1-phenylethanol in 93% yield and 98% enantiomeric excess. Wang

Figure 2



studied the preparation and synthetic use of lanthanide(III) catalysts supported on ion exchange resins.[33] A number of commercially available ion exchange resins were loaded with lanthanide(III) ions and their capacity of catalyzing Mukaiyama aldol reactions has been tested. The reaction of benzaldehyde with a silyl enol ether in dichloromethane in the presence of Yb(III) loaded on various resins were performed with overall yields ranging from 71-83%. Soai reported the use of immobilized *N*-butylnorephedrine (**82**) as a catalyst in enantioselective addition of diethylzinc to various aldehydes producing secondary alcohols.[34] It is interesting to note that the best result was obtained in hexane with 53-91% yield and 51-82% ee of enantioselectivity. The works on organic transformation using solid-supported catalysts in water are very limited to the isolated instances reported by Bergbreiter in 1997.[6] To the best of our knowledge, catalytic asymmetric reaction in water by use of solid-supported chiral catalyst has never been reported so far.

Survey of Thesis

This thesis is constituted of four chapters.

Chapter I deals with design and preparation of amphiphilic resin-supported phosphine-palladium complexes. Resin-supported phosphine was prepared by dehydrative condensation of diphenylphosphinobenzoic acid with PEG-PS amino resin. Treatment of the resin-supported phosphines with di(μ-chloro)bis(η^3-allyl)dipalladium gave resin-supported palladium complexes quantitatively. The structure of these phosphines and palladium-phosphine complexes were studied by ^{31}P NMR measurement.

The next two chapters are concerned with the application of amphiphilic resin-supported complexes prepared in chapter I to typical palladium-catalyzed reactions.

Chapter II deals with allylic substitution of allylic compounds catalyzed by amphiphilic resin-supported phosphine-palladium complexes with various nucleophiles such as 1,3-dicarbonyl compounds in genuine aqueous media. A resin-supported complex catalyzed the reaction of 1,3-diphenylphosphino-2-acetoxypropene with ethyl acetoacetate in potassium carbonate aqueous solution at room temperature to give 4-ethoxycarbonyl-1,3-diphenyl-1-hexen-5-one in 98% yield.

Chapter III deals with arylation of aryl halide and allyl acetate with arylboronic acid catalyzed by the amphiphilic resin-supported complex in aqueous media at room temperature. Allyl acetate with substituents at C1 and C3 position also underwent resin-supported complex-catalyzed allylic arylation with arylboron reagent in aqueous solution of potassium carbonate at room temperature.

Chapter IV deals with preparation of amphiphilic resin-supported MOP-palladium complexes and their use for asymmetric allylic substitution reaction n aqueous media. The carboxylated MOP derivatives were condensed with a terminal amino residue of PEG chain on the resin. Various amino acids were incorporate between a supported MOP ligand and the terminal amino residue as diversity elements. Palladium complexes of resin-supported MOP were applied for allylic substitution of 1,3-diphenyl-2-acetoxypropene with 3-methyl-2,4-pentanedione to give 4-acetoxy-4-methyl-1,3-diphenyl-1-hexen-5-one of up to 84% ee.

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Chapter I

Design and Preparation of New Amphiphilic Palladium-Phosphine Complexes Bound to Solid Support

Summary: New amphiphilic palladium-phosphine complexes (**8**) were designed and prepared on polyethylene glycol-polystyrene graft copolymer (PEG-PS) resin by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) and PEG-PS resin supported triarylphosphine (**7**) synthesized from 4-(diphenylphosphino)benzoic acid and PEG-PS amino resin.

Introduction

It is one of the most important issue to develop organic transformation processes in accordance with saving natural resources and environmental protection.[1] Water is one of the most suitable solvent for organic chemistry in next generation owing to its safety and harmlessness. Development of immobilized reagents has been attracting significant interest for their practical advantages.[2] There is good reason to believe that immobilized reagents exhibiting high reactivity in aqueous media offer a viable clean alternative to more traditional methods of accomplishing many organic reactions.[3,4,5] On the other hand, transition metal complexes, palladium-phosphine complexes in particular, find widespread utilities as catalysts for a variety of organic reactions.[6] In contrast to the vast amount of research on the palladium-catalyzed reactions in organic solvents, only scattered attention has been paid to those in aqueous media. Providing that the palladium-

Table 1. Swelling volume of polystyrene, crosslinked with 1% DVB (dry volume: 1.6 mL/g) and TentaGel resin (dry volume: 1.7 mL/g)[a]

Solvent	H_2O	MeOH	CH_2Cl_2	Toluene	DMF	MeCN	THF
polystyrene 1% DVB	–	1.6	8.3	8.5	5.6	3.2	8.8
TentaGel resin	4.25	4.25	5.1	5.3	5.4	5.1	5.8

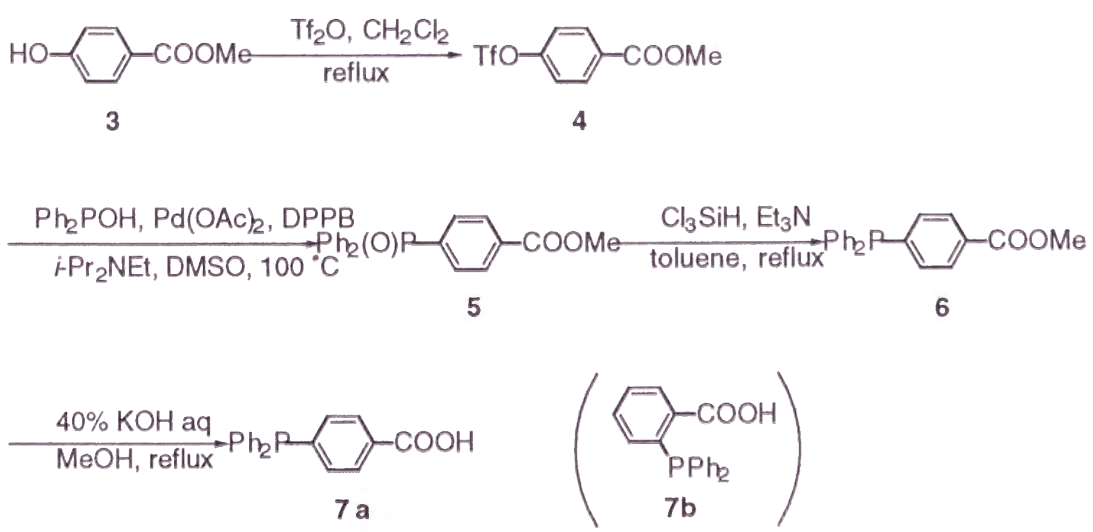
[a] For measuring the swelling volume, 1 g of resin was swollen the solvent for 24 h.

catalyzed reaction proceeds in water, it would be one of the most powerful method for organic synthesis. In this chapter I report the strategy for design and preparation of a new classes of palladium-phosphine complexes bound to an amphiphilic polymer resin, which were expected to exhibit the activity for palladium-catalyzed reaction in aqueous media.

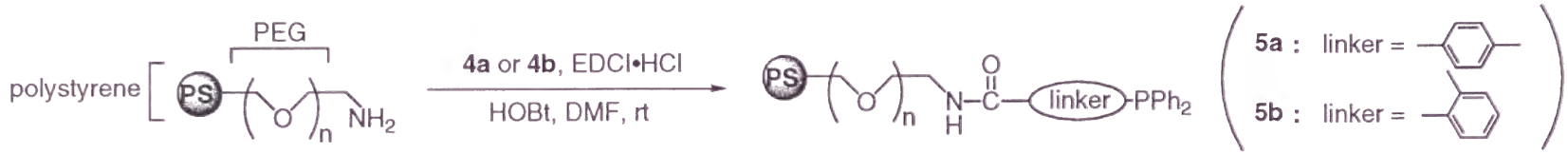
Results and Discussion

With the advance of the synthetic organic chemistry on solid phase, a large number of polymer supports with various properties were researched and developed.[7b] It has been well-documented that polymer resin based on a polyethylene glycol-polystyrene graft copolymer (PEG-PS) exhibits good swelling properties in water as well as in organic solvents (Table 1).[7b] Although polystyrene swells in dichloromethane and DMF with > 8 mL/g of swelling volume, only slight swelling properties are observed in methanol and water. PEG-PS resin (TentaGel) shows good swelling properties in dichloromethane (5.1 mL/g), DMF (5.4 mL/g), methanol (4.25 mL/g), and water (4.25 mL/g). PEG-PS resin having amino group of 0.123 mmol/g of loading value (TentaGel S NH_2) (**1**)[7] was examined as amphiphilic resin to prepare polymer-supported palladium-triarylphosphine complexes. Triarylphosphino group was supported on polymer resin by means of dehydrative condensation of 4-(diphenylphosphino)benzoic acid (**2a**) with terminal amino residue of PEG chain on the resin (Scheme 1). Methyl 4-hydroxybenzoate (**3**) was converted into methyl 4-(trifluoromethanesulfonyl)oxybenzoate **4** by treatment with triflic anhydride and pyridine in dichloromethane at ambient

Scheme 1

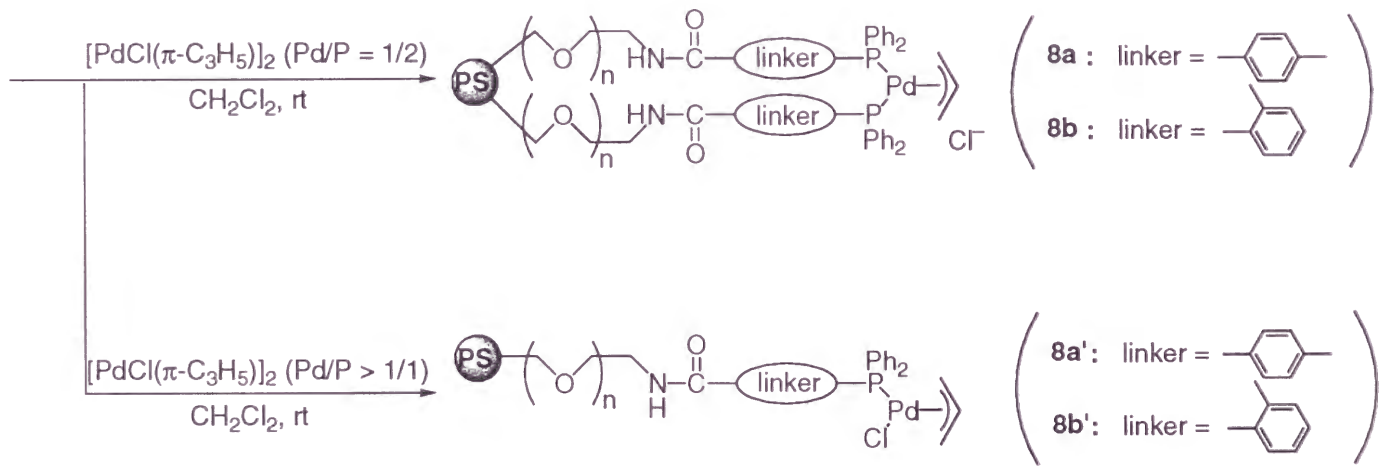


Scheme 2



PEG-PS Amino Resin (TentaGel S-NH_2) (**1**)

PEG-PS resin-supported Phosphine (PEP) (**7a,b**)



Palladium-PEG-PS resin-supported Phosphine Complex (Pd-PEP) (**8a,b** and **8a',b'**)

temperature in 94% yield. Palladium-catalyzed phosphinylation of **4** with diphenylphosphine oxide in the presence of palladium-dppb complex gave methyl 4-(diphenylphosphinyl)benzoate **5** in 93% yield.[8] Reduction of phosphine oxide by trichlorosilane and triethylamine gave 65% of methyl 4-(diphenylphosphino)benzoate **6**.[9] Hydrolysis of **6** with aqueous potassium hydroxide in refluxing methanol gave **2a** in 95% yield. Preparation of 2-(diphenylphosphino)benzoic acid (**7**) was performed according to the procedure reported by Trost.[10] The phosphinobenzoic acid **2** was attached to PEG-PS amino resin by amide bond formation reaction (Scheme 2). Thus, a mixture of PEG-PS amino resin (1.0 g), 2 equiv of **2**, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI•HCl) (3 equiv), and 1-hydroxybenzotriazole (HOBt) (4 equiv) in DMF was agitated with shaking on a wrist-action shaker at ambient temperature for 4 h. The resin was washed 5 times with DMF (20 mL) and 8 times with dichloromethane (30 mL), and then dried under reduced pressure. A negative Kaiser test indicated that the condensation was completed to form polymer-supported triarylphosphine **7a** quantitatively.[11] According to the same procedures, polymer-supported phosphine **7b** which bound to the solid support by an ortho substituted aromatic linker was prepared from 2-(diphenylphosphino)benzoic acid **2b** quantitatively.

The gel-phase ^{31}P NMR study of resin-supported phosphines dispersed in chloroform were performed by use of the standard solution-phase parameters.[12] A narrow singlet at δ –5.1 ppm was observed for the spectrum of **7a** in $CDCl_3$ (Figure 1, a). Polystyrene supported triphenylphosphine **9** gave a resonance at δ –7.8 ppm in $CDCl_3$ as a broad singlet (b). The spectrum of **7a** could also be observed as a narrow singlet in water at δ –7.2 ppm (c), while the resonance of **9** in water was extremely broadened as shown in Figure 1 (d). Since the functional group of PEG-PS resin is located far away from the rigid polystyrene matrix by long and flexible polyethylene glycol chain, it has been postulated that the molecules attached to the ends of the PEG chain are in a "solution like" environment. The gel-phase ^{31}P NMR of PEG-PS resin-supported phosphine giving relatively sharp signals demonstrates excellent mobility of the phosphine moiety bound to the resin.

Formation of palladium-phosphine complex on the resin was performed by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) and **7a**. The reaction progress was conveniently monitored by gel-phase ^{31}P NMR spectroscopy. The reaction with 0.5 equiv to phosphorus of palladium in dichloromethane at ambient temperature for 10 min gave resin -bound phosphine-palladium complex where singlet at δ –5.1 ppm observed for **7a** disappeared and was replaced by a new resonance at δ +24.8 ppm. This remarkable low field shift demonstrates that the phosphino group of **7a** coordinates to palladium forming a π-allylpalladium-phosphine complex (**8a**). The reaction with 1.1 equiv palladium to the phosphine gave complex **8a'**, which showed the resonance at δ +23.2 ppm in the gel-

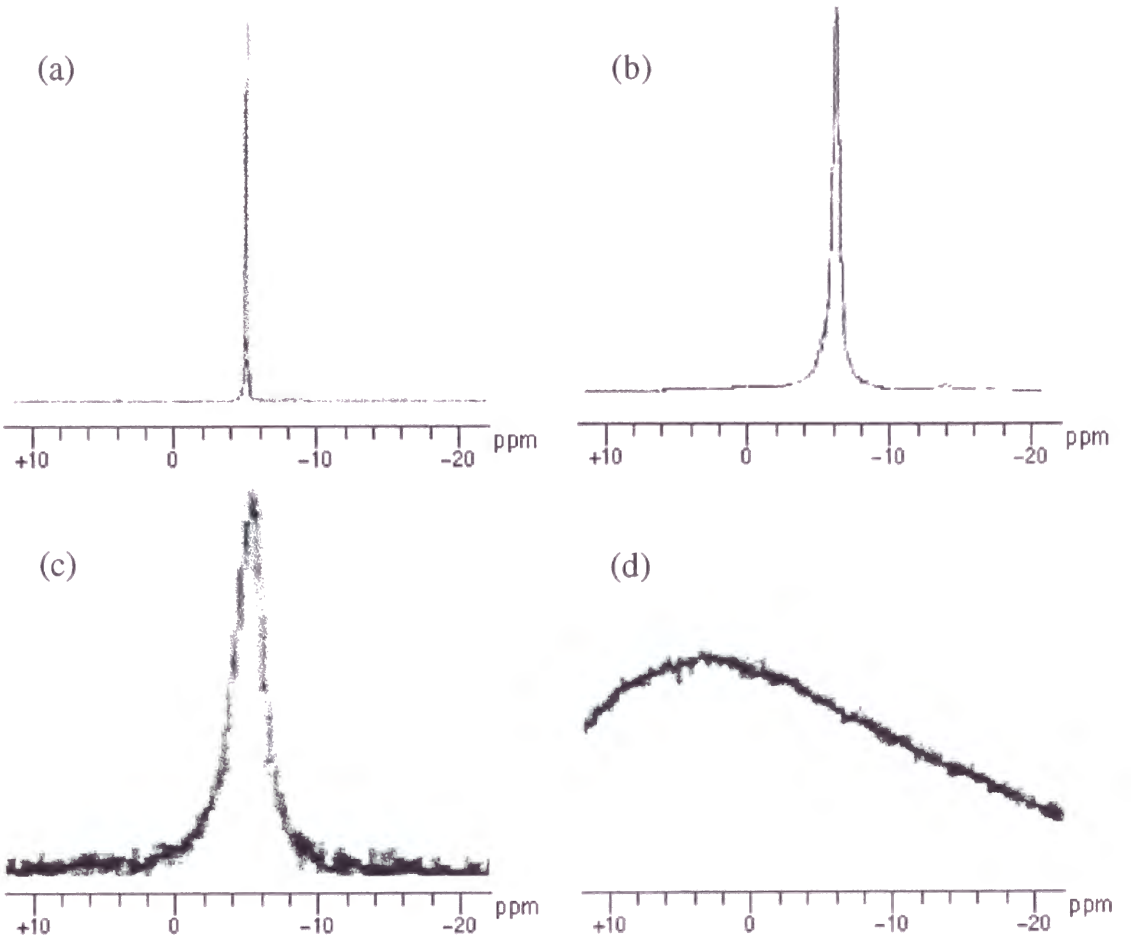


Figure 1. ^{31}P NMR spectra of resin-supported phosphines: (a) PEG-PS supported phosphine **7a** in $CDCl_3$. (b) Polystyrene-supported triphenylphosphine in $CDCl^3$ (c) **7a** in H_2O. (d) Polystyrene-supported triphenylphosphine in H_2O.

phase ^{31}P NMR spectroscopy. The gel-phase ^{13}C NMR spectrum of **8a'** exhibit a singlet signal at 61.4 ppm, and two doublet signals at 80.0 ppm ($^2J_{C-P}$ = 31 Hz) and 118.3 ppm ($^2J_{C-P}$ = 5 Hz), demonstrating that its structure is PdCl(η^3-allyl)(phosphine).[13] Complexes **8b** and **8b'** were prepared from **7b** according to the same procedures. Complexes **8a**, **8a'**, **8b**, **8b'** also showed good swelling properties in water. These complexes are expected to exhibit high catalytic activity both in water and organic solvents owing to their solution-like properties.

Experimental Section

General. All manipulations were carried out under nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JMN-EX270 spectrometer (270 MHz for ^1H and 109 MHz for

^{31}P), JEOL JMN-AL400 spectrometer (400 MHz for ^{1}H), JEOL JMN-LA400 spectrometer (400 MHz for ^{1}H), or JEOL JMN-LA500 spectrometer (500 MHz for ^{1}H and 202 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR, and to an external 85% H_3PO_4 standard for ^{31}P NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. ^{1}H, ^{13}C, ^{31}P, NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. The agitation of the reaction mixture was performed on a wrist-action shaker (Burrel Scientific, Inc.).

Materials. Tetrahydrofuran was dried over sodium benzophenone ketyl and distilled prior to use. DMF and dichloromethane was dried over calcium hydride and distilled prior to use. TentaGel S NH_2 was purchased from Rapp Polymere (Germany) and washed with acetonitrile (6 × 20 mL, 15 min for 1g of resin) and chloroform (5 × 20 mL, 5 min for 1 g of resin) prior to use. Methyl 4-hydroxybenzoate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI•HCl) and 1-hydroxybenzotriazole (HOBt) were purchased from Nacalai Tesque Co. Inc. 1,4-Bis(diphenylphosphino)butane was purchased from Tokyo Chemical Industry Co. Inc. Triphenylphosphine, polymer supported (**9**) was purchased from Aldrich Co. Inc. *Ortho*-diphenylphosphinobenzoic acid (**2b**)[10] and diphenylphosphine oxide[8] was prepared according to reported procedures.

Methyl 4-(trifluoromethanesulfonyl)oxybenzoate (4).[14] To a solution of methyl 4-hydroxybenzoate (**3**) (7.61 g, 50.0 mmol) and pyridine (5.20 mL, 65.0 mmol) in dichloromethane (200 mL) was added trifluoromethanesulfonic anhydride (10.1 mL, 60.0 mmol) at 0 °C and the mixture was stirred for 6 h. After the reaction mixture was condensed under reduced pressure, the residue was diluted with 150 mL of EtOAc and the organic layer was washed with 1% HCl, saturated $NaHCO_3$, and brine (once for each). The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to give 13.3 g (94%) of **4** as a colorless oil: ^{1}H NMR δ 3.94 (s, 3H), 7.36 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H).

Methyl 4-(diphenylphosphinyl)benzoate (5).[14] To a mixture of **4** (13.6 g, 47.9 mmol), diphenylphosphine oxide (15.9 g, 78.6 mmol), palladium diacetate (1.08 g, 4.80 mmol), and 1,4-bis(diphenylphosphino)butane (2.05 g, 4.80 mmol) were added 200 mL of dimethyl sulfoxide and diisopropylethylamine (33.4 mL, 192 mmol), and the mixture was heated with stirring at 100 °C for 12 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: EtOAc) to give 15.0 g (93%) of **5** as a white solid: ^{1}H NMR δ 3.93 (s, 3H), 7.40-7.80 (m, 12H), 8.12 (d, J = 8.5 Hz, 2H); $^{31}P\{^{1}H\}$ NMR δ 28.9.

Methyl 4-(diphenylphosphino)benzoate (6).[14] To a mixture of **5** (8.41 g, 25.0 mmol) and triethylamine (64.0 mL, 460 mmol) in toluene (500 mL) was added

trichlorosilane (12.0 mL, 120 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After being cooled to room temperature, the mixture was diluted with 300 mL of ether and quenched with small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite, and the filter cake was washed 3 times with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 5.18 g (65%) of **6** as a white solid: ^{1}H NMR δ 3.89 (s, 3H), 7.24-7.39 (m, 12H), 7.96 (d, J = 8.1 Hz, 2H); ^{31}P{^{1}H} NMR δ –4.5.

4-(Diphenylphosphino)benzoic acid (2a).[14] To a solution of **6** (5.18 g, 16.2 mmol) in 200 mL of methanol was added 40% aqueous potassium hydroxide solution (40.0 mL) at ambient temperature and the reaction mixture was refluxed for 12 h. The solution was acidified (pH = 2) by addition of conc. HCl and then extracted 3 times with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give 4.69 g (95%) of **2a** as a white solid: ^{1}H NMR δ 7.33-7.37 (m, 12H), 8.03 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR δ 128.7, 128.8, 129.1, 129.2, 129.8, 129.9, 133.1, 133.3, 133.9, 134.1, 171.8; ^{31}P{^{1}H} NMR δ –4.4.

Preparation of Amphiphilic Solid-Supported Phosphine 7a,b. A Merrifield vessel was charged with TentaGel S NH_2 (**1**) (1.00 g, 0.123 mmol/g), **2a** (135 mg, 0.44 mmol), EDCI•HCl (127 mg, 0.66 mmol), HOBt (119 mg, 0.88 mmol), and DMF (20.0 mL) and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 4 h. The reaction mixture was filtered and the resin was washed with DMF (5 × 20 mL) and dichloromethane (8 × 20 mL). The resin was dried under reduced pressure to give **7a:** ^{31}P{^{1}H} (gel-phase) NMR δ –5.1 (s); **7b**: ^{31}P{^{1}H} NMR (gel-phase) δ –8.8 (s).

Preparation of Palladium-PEP Complex 8a and 8a',b'. A Merrifield vessel was charged with 1.04 g of resin-supported phosphine **7a** (loading value: 0.123 mmol/g) and 20.0 mL of dichloromethane. To a suspension was added 22.5 mg of di(μ-chloro)bis(η^3-allyl)dipalladium(II) (62.0 μmol) at room temperature and the mixture was shaken on a wrist-action shaker at 25 °C for 10 min. After filtration, the resin was washed with dichloromethane (3 × 20 mL) and dried under reduced pressure to give 1.06 g of **8a:** ^{13}C{^{1}H} NMR (gel phase) δ 39.9, 61.4, 69.7, 70.6, 80.0 (d, J = 30.5 Hz), 118.3 (d J = 5.0 Hz), 127.2, 127.3, 128.8 (d, J = 9.9 Hz), 130.8, 131.6, 132.0, 134.0 (d, J = 11.5 Hz), 136.5, 166.7; ^{31}P{^{1}H} NMR (gel-phase) δ 23.2 (s); **8b**: ^{31}P{^{1}H} NMR (gel-phase) δ 25.9 (s).

Measurement of NMR Spectra of Resin-Supported Phosphine 7 and Complex 8. In an NMR sample tube were placed **7** of **8** (30 mg). The tube was filled with nitrogen and $CDCl_3$ (0.4 mL) was added. ^{31}P NMR spectra for **7a**, **7b**, **8a**, **8a'**, and **8b'** and a ^{13}C NMR spectrum for **8a'** were measured.

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14. CAS numbers for these compounds are supplied as follows; **2a**: [2129-31-9], **4**: [17763-71-2], **5**: [5032-55-3], **6**: [5032-51-9]

Chapter II

Catalytic Allylic Substitution in Water by Use of Amphiphilic Polymer-Supported Palladium-Phosphine Complexes

Summary: An amphiphilic solid-supported phosphine-palladium complex (**1a**) containing polyethylene glycol chain between polystyrene polymer support and phosphine-palladium complex catalyzed allylic alkylation of allyl esters with various nucleophiles including 1,3-dicarbonyl compounds to give alkylation products in 68 to 100% yield.

Introduction

Owing to increasing environmental concerns about harmful and resource-consuing solvent waste,[1] the chemistry of organic transformation in water is presently undergoing very rapid growth.[2] Over the past three decades the chemistry of transition metal-catalyzed reactions has been intriguing a large number of chemists. In particular, remarkable development have been achieved in the catalytic reactions with palladium-phosphine complexes.[3] My research interests, recently, lie in the development of transition metal-catalyzed organic transformations in aqueous media which would provide a safety, resource-saving, and environmentally benign process.[4,5] It has been well-documented that palladium-phosphine complexes are able to exhibit catalytic activity in aqueous organic solvent,[4,5] and the tolerance of palladium complexes to many functional group such as carbonyl and hydroxy groups makes themselves very versatile catalysts for various organic transformation.[3]

In the previous chapter, resin-supported phosphine-palladium complexes were designed and prepared.[6] The resin-supported complexes bound to a polystyrene-polyethylene glycol graft copolymer (PEG-PS resin) exhibit good swellig properties in water as well as organic solvents owing to the amphiphilicity of PEG resin. The amphiphilic solid-supported phosphine-palladium complexes are expected to realize

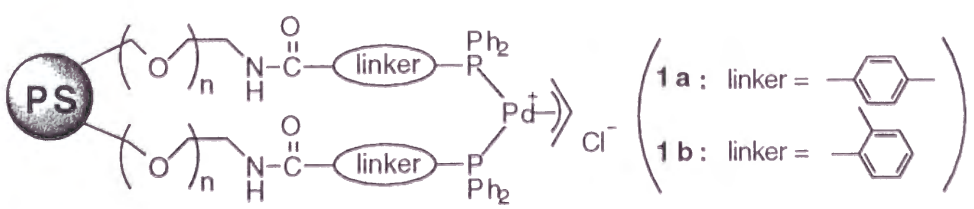

Figure 1. Palladium-PEG-PS resin supported Phosphine Complex (Pd-(PEP)$_2$) (**1a,b**)

palladium-catalyzed organic transformations in water.[5,6] The palladium-catalyzed allylic substitution of allyl esters constitutes one of the most powerful methods in catalytic organic transformations.[3] I describe in this chapter the application of the amphiphilic solid-supported phosphine-palladium complexes for allylic substitution of allyl acetates with various nucleophiles in aqueous media.[7]

Results and Discussion

The palladium-phosphine complex **1a** bound to amphiphilic solid supports demonstrated its high catalytic activity in the allylic substitution of 1,3-diphenyl-2-acetoxypropene (**2**) in aqueous media under very mild conditions (Scheme 1, Table 1).

Scheme 1

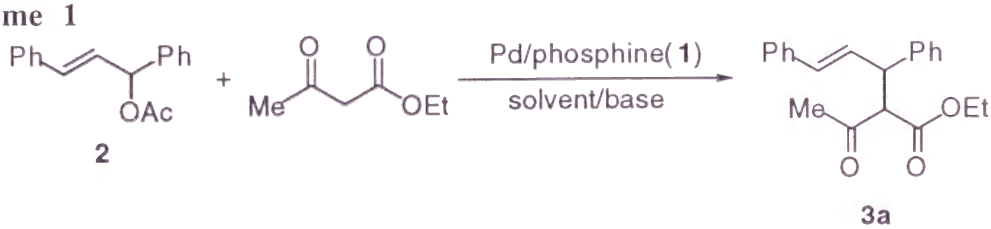

Table 1. Allylic Substitution of **2** with Ethyl Acetoacetate Catalyzed by Solid-Supported Palladium-Phosphine Catalyst **1**[a]

entry	catalyst	solvent	base	yield (%)[b]
4	**1a**	H_2O	K_2CO_3	98
2	**1a**	THF	K_2CO_3	6
3	**1a**	H_2O	DBU	28
1	**1a**	THF	DBU	17
5[c]	**1b**	H_2O	K_2CO_3	22
6	Pd-TPPTS[d]	H_2O	K_2CO_3	–[e]
7	Pd-PPh_3[f]	THF	DBU	6

[a] The reaction was carried out in tetrahydrofuran (THF) or H_2O with 1.5 equiv of ethyl acetoacetate and 4.5 equiv of base in the presence of 2 mol % of a catalyst at room temperature for 12 h. **1** (g)/H_2O (mL) = 1/15. [b] Isolated yield by silica gel column chromatography. [c] Carried out at 85 °C. At room temperature, the yield of **3a** was 2%. [d] A catalyst generated in situ by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) and TPPTS (Pd/P = 1/2) was used. [e] No reaction. Starting material **2** was recovered quantitatively. [f] A catalyst generated in situ by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) and triphenylphosphine (Pd/P = 1/2) was used.

A mixture of **2** (0.5 mmol), ethyl acetoacetate (1.5 equiv), and potassium carbonate (4.5 equiv) in 1.5 mL of water was shaken in the presence of 2 mol % palladium of resin-supported catalyst **1a** at ambient temperature for 12 h. The reaction mixture was filtered and the resin was rinsed with chloroform. The combined filtrate was concentrated and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 4-carboethoxy-1,3-diphenyl-1-hexen-5-one (**3a**) in 98% yield (Table 1, entry 1). It is noteworthy that potassium carbonate is an effective base in water for the present allylic alkylation catalyzed by **1a**. The reaction in THF gave 6% yield of **3a** under the same reaction conditions (entry 2). Complex **1a** was much less catalytically active in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) as a base in H_2O or THF (entries 3 and 4). In general, the palladium-catalyzed alkylation with active methylene or methine compounds requires a stronger base; e.g. sodium hydride or tertiary amines.[4] It has been reported that palladium-phosphine complexes catalyze alkylation of allylic acetates with β-ketoesters in the presence of potassium carbonate or DBU as a base in an organic solvent (e.g. THF, dioxane, or toluene) where much higher reaction temperature is required than the temperature in the reaction catalyzed by **1a** in water.[8] The catalytic activity of **1b** was lower than that of **1a** in the present reaction (entry 5). With a water soluble phosphine ligand, 3,3',3"-phosphinidynetris(benzenesulfonic acid), trisodium salt (TPPTS),[4a-g] the alkylation did not proceed under the same conditions (entry 6). The allylic alkylation in the presence of palladium-triphenylphosphine complex generated in situ by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II) and triphenylphosphine (Pd/P = 1/2) and DBU as a base in THF gave 6% yield of **3a** at room temperature (entry 7).

Scheme 2

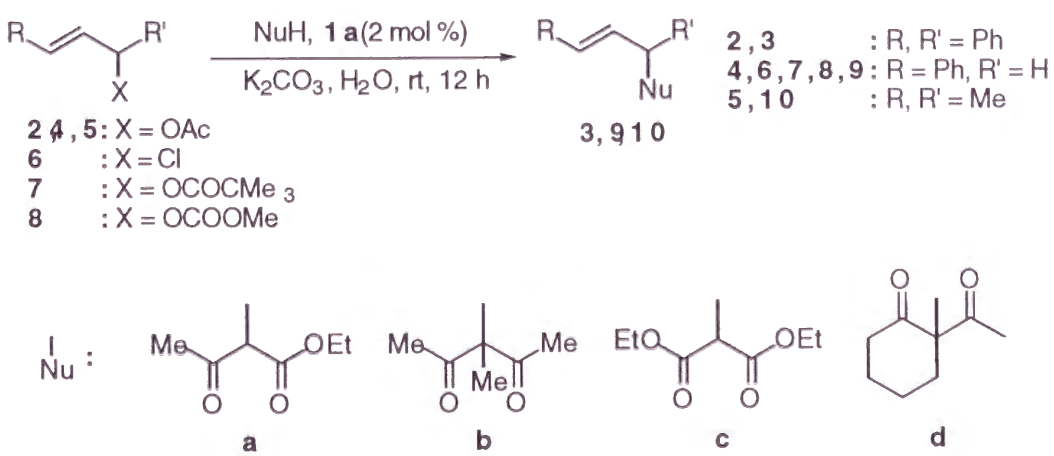

Table 2. Allylic Substitution of Allyl Acetates with 1,3-Dicarbonyl Compounds Catalyzed by **1a**[a]

entry	allylic compound	nucleophile	product	yield (%)[b]
1	**2**	CH_3COCH_2COOEt	**3a**	98
2	**2**	$CH_3CH(COCH_3)_2$	**3b**	86
3	**2**	$(O=)C_6H_9COOEt$	**3c**	100
4	**2**	$CH_2(COOEt)_2$	**3d**	94
5	**4**	CH_3COCH_2COOEt	**9a**	89[d]
6	**4**	$CH_3CH(COCH_3)_2$	**9b**	100[c]
7	**4**	$(O=)C_6H_9COOEt$	**9c**	95
8	**5**	CH_3COCH_2COOEt	**10a**	88
9	**6**	$CH_3CH(COCH_3)_2$	**9b**	72
10	**7**	$CH_3CH(COCH_3)_2$	**9b**	68
11	**8**	$CH_3CH(COCH_3)_2$	**9b**	71

[a] The reaction was carried out in H_2O with 1.5 equiv of a nucleophile and 4.5 equiv of potassium carbonate in the presence of 2 mol % of **1a** at room temperature for 12 h. **1a** (g)/H_2O (mL) = 1/15. [b] Isolated yield by silica gel column chromatography. [c] Including 11% of 4-methyl-1-phenyl-1-hexen-5-one. [d] Including 24% of ethyl 5-phenyl-4-hexenoate.

Various nucleophiles could be employed for the allylic substitution of allyl acetates catalyzed by **1a** in water (Scheme 2). The representative results are summarized in Table 2. The allylic alkylation of 1,3-diphenyl-2-acetoxypropene (**2**) with 3-methyl-2,4-pentanedione, ethyl 2-cyclohexanonecarboxylate, and diethyl malonate took place in water under the same reaction conditions to give **3b**, **3c**, and **3d** in 86, 100, and 94% yield, respectively (entries 2-4). Cinnamyl acetate (**4**) and 2-acetoxy-3-pentene (**5**) also underwent the alkylation to give **9** and **10** in high yields (entries 5-8). The palladium-catalyzed allylic substitution of cinnamyl chloride (**6**), cinnamyl trimethylacetate (**7**), and cinnamyl methyl carbonate (**8**) with 3-methyl-2,4-pentanedione also proceeded to form **9b** in 72%, 68%, and 71% yield under the same reaction conditions, respectively (entries 9-11).

This allylic substitution method was also successfully applied to other nucleophiles which are insoluble or almost insoluble in usual organic solvents (Table 3). With hydrochloride salts of leucine and phenylalanine ethyl esters, amination of **2** took place at room temperature under the same reaction conditions to give the corresponding *N*-

Scheme 3

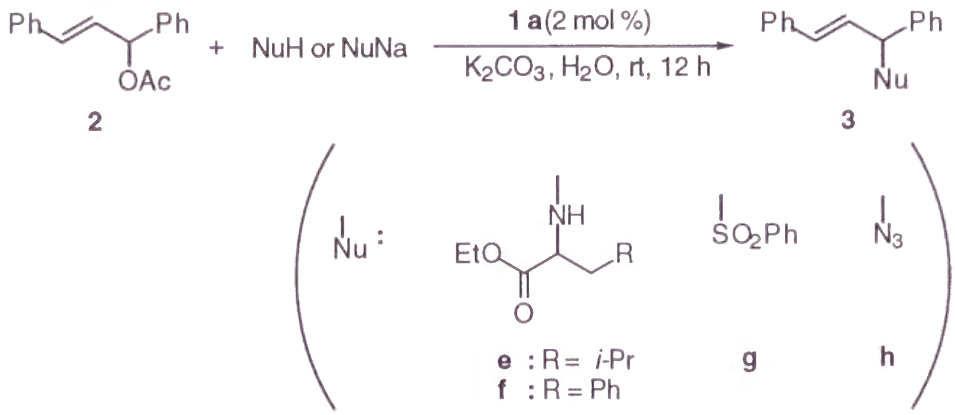

Table 3. Allylic Substitution of **2** with Nucleophiles Insoluble in Organic Solvents Catalyzed by **1a**[a]

entry	NuH (or NuNa)	base	product	yield (%)[b]
1	Leu-OEt•HCl	K_2CO_3	**3e**	98
2	Phe-OEt•HCl	K_2CO_3	**3f**	90
3	$PhSO_2Na$	none	**3g**	86
4	NaN_3	none	**3h**	79

[a] The reaction was carried out in H_2O with 1.5 equiv of a nucleophile and 6 equiv or absence of base in the presence of 2 mol % of a catalyst at room temperature for 12 h. **1** (g)/H_2O (mL) = 1/15. [b] Isolated yield by silica gel column chromatography.

allylation products **3e** and **3f** in 98% and 90% yields, respectively (entries 1 and 2).[9] Sodium phenylsulfinate and sodium azide reacted with **2** to give allyl sulfone **3g** and allyl azide **3h** in high yields (entries 3 and 4).[10,11]

The solid-supported catalysts can be readily recovered and reused by filtration (Figure 2). Thus, after the reaction of ethyl acetoacetate with **2** the reaction mixture was filtered and the catalyst-resin **1a** was rinsed twice with THF. High yield of **3a** was obtained from the combined filtrate and the recovered **1a** was subjected to the next series of the reaction. The second use of the catalyst gave again **3a** in 99% yield. The recycle of the catalyst was repeated 6 times (1st-7th use) during which no loss of catalytic activity was observed. The chemical yield observed in the 7 continuous runs ranged from 86 to 99%, the average being 95% yield.

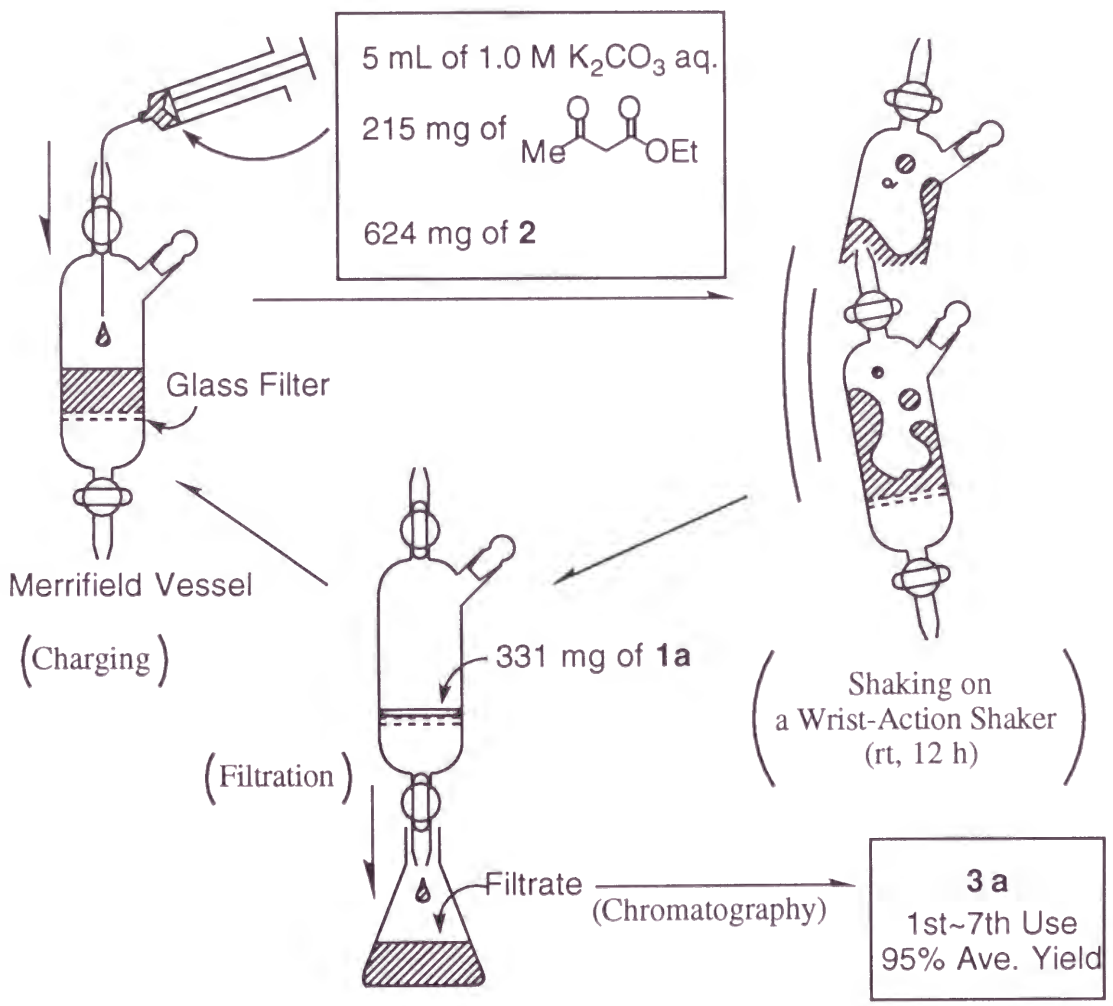

Figure 2. Schematic representation of the recycle experiment.

Experimental Section

General. All manipulations were carried out under nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JMN-EX270 spectrometer (270 MHz for ^1H), JEOL JMN-LA400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C), or JEOL JMN-LA500 spectrometer (500 MHz for ^1H). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. The agitation of the reaction mixture was performed on a wrist-action shaker (Burrel Scientific, Inc.).

Materials. THF was dried over sodium benzophenone ketyl and distilled prior to use. Water was distilled prior to use. Pd-$(PEP)_2$ catalyst (**1a,b**) was prepared on commercially available polystyrene-polyethylene graft copolymer beads, TentaGel S-NH_2 (Rapp Polymere, Germany) according to the procedure reported in chapter I. 1,3-Diphenyl-1-acetoxy-2-propene (**2**),[12] 2-acetoxy-3-pentene (**5**),[13] cinnamyl trimethylacetate (**7**),[13] and cinnamyl methyl carbonate (**8**)[13] were prepared according to the reported procedures. Cinnamyl acetate (**4**), cinnamyl chloride (**6**), L-leucine ethyl ester hydrochloride, and 1,8-diazabicyclo[5.4.0]-7-undecene were purchased from Tokyo Chemical Industry Co. Inc. Ethyl acetoacetate and diethyl malonate were purchased from Wako Chemical Co. Inc. 3-Methyl-2,4-pentanedione, ethyl 2-cyclohexanonecarboxylate, sodium phenylsulfinate, and 3,3',3"-phosphinidynetris(benzenesulfonic acid), trisodium salt (TPPTS) were purchased from Aldrich Co. Inc. L-Phenylalanine ethyl ester hydrochloride was purchased from Nacalai Tesque Co. Inc. Ethyl 2-carboethoxy-3,5-diphenyl-4-pentanoate (**3d**),[13] *N*-(1,3-diphenyl-2-propenyl)leucine ethyl ester (**3e**),[9,13] ethyl 2-acetyl-5-phenyl-4-pentenoate (**9a**),[11] and 3-carboethoxy-4-methyl-5-hepten-2-one (**10a**)[13] are known compounds.

Allylic Substitution with Solid-Supported Palladium-Phosphine Catalyst. Method A. A typical procedure is given for the reaction of 3-acetoxy-1,3-diphenyl-1-propene (**2**) and ethyl acetoacetate (Table 1, entry 1). A Merrifield vessel was charged with potassium carbonate (311 mg, 2.30 mmol), **1a** (100 mg, 10.0 μmol Pd) and 1.50 mL of water. To the mixture was added ethyl acetoacetate (98 mg, 0.75 mmol) and **2** (126 mg, 0.50 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 158 mg (98%) of 4-carboethoxy-1,3-diphenyl-1-hexen-5-one (**3a**) as a 1:1 mixture of diastereoisomers: ^1H NMR δ 0.98 (t, J = 7.3 Hz, 1/2H × 3), 1.21 (t, J = 7.3 Hz, 1/2H × 3), 2.04 (s, 1/2H × 3), 2.30 (s, 1/2H × 3), 3.94

(q, J = 7.3 Hz, 1/2H × 2), 4.08 (d, J = 11.2 Hz 1/2H), 4.11 (d, J = 11.2 Hz 1/2H), 4.17 (q, J = 7.3 Hz, 1/2H × 2), 4.29 (dd, J = 7.9, 11.2 Hz, 1H), 6.24 (dd, J = 7.9, 15.8 Hz, 1/2H), 6.29 (dd, J = 7.9, 15.8 Hz, 1/2H), 6.43 (d, J = 15.8 Hz, 1/2H), 6.46 (d, J = 15.8 Hz, 1/2H), 7.17-7.43 (m, 10H); $^{13}C\{^1H\}$ NMR δ 13.8, 14.2, 29.8, 30.0, 48.7, 49.0, 61.4, 61.6, 65.3, 65.6, 126.3, 126.4, 127.1, 127.2, 127.5, 127.6, 127.97, 128.02, 128.5, 128.7, 128.9, 129.3, 129.5, 131.5, 131.8, 136.7, 136.9, 140.2, 140.4, 167.6, 167.9, 201.4, 201.7; Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.04; H, 6.78.

4-Acetyl-4-methyl-1,3-diphenyl-1-hexen-5-one (3b): ^1H NMR δ 1.49 (s, 3H), 1.93 (s, 3H), 2.16 (s, 3H), 4.69 (d, J = 8.1 Hz, 1H), 6.39 (dd, J = 8.1, 15.6 Hz 1H), 6.46 (d, J = 15.6 Hz, 1H), 7.17-7.32 (m, 10H); $^{13}C\{^1H\}$ NMR δ 15.9, 27.5, 27.9, 51.6, 71.6, 126.4, 127.1, 127.6, 127.9, 128.4, 128.5, 129.6, 133.2, 136.9, 139.8, 205.7, 206.5; Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.29; H, 7.32.

2-Carboethoxy-2-(1,3-diphenyl-2-propenyl)-cyclohexan-1-one (3c): As a 1:1 mixture of diastereomers. ^1H NMR δ 1.06 (t, J = 7.3 Hz, 1/2H × 3), 1.07 (t, J = 7.3 Hz, 1/2H × 3), 1.48-1.76 (m, 4H), 1.89-1.99 (m, 1H), 2.40-2.47 (m, 1/2H × 5), 2.58-2.62 (m, 1/2H × 1), 3.88-4.05 (m, 2H), 4.09 (d, J = 9.5 Hz, 1/2H × 1), 4.24 (d, J = 8.8 Hz, 1/2H × 1), 6.39 (d, J = 15.8 Hz, 1/2H × 1), 6.39 (d, J = 15.8 Hz, 1/2H × 1), 6.69 (dd, J = 8.8, 15.8 Hz, 1/2H × 1), 6.71 (dd, J = 9.5, 15.8 Hz, 1/2H × 1), 7.16-7.43 (m, 10H); $^{13}C\{^1H\}$ NMR δ 22.7, 26.7, 27.1, 33.7, 35.2, 41.9, 42.0, 53.1, 53.8, 61.3, 65.8, 66.0, 126.3, 126.4, 126.8, 126.9, 127.2, 127.3, 128.0, 128.1, 128.41, 128.43, 129.1, 129.4, 129.9, 130.2, 132.3, 137.3, 137.4, 139.8, 140.0, 170.78, 170.80, 206.4, 206.7; Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.28; H, 7.20.

***N*-(1,3-Diphenyl-2-propenyl)phenylalanine ethyl ester (3f):** As a 1.2:1 mixture of diastereoisomers. ^1H NMR δ 1.12 (t, J = 7.3 Hz, 1.2/2.2H × 3), 1.16 (t, J = 7.3 Hz, 1/2.2H × 3), 2.91-2.97 (m, 2H), 3.40 (t, J = 7.3 Hz, 1.2/2.2H × 1), 3.68 (t, J = 7.3 Hz, 1/2.2H × 1), 4.01-4.12 (m, 2H), 4.31 (t, J = 7.6 Hz, 1H), 6.09 (dd, J = 7.6, 15.9 Hz, 1/2.2H × 1), 6.21 (dd, J = 7.6, 15.9 Hz, 1.2/2.2H × 1), 6.46 (t, J = 14.9 Hz, 1H), 7.14-7.38 (m, 15H); $^{13}C\{^1H\}$ NMR δ 14.2, 40.1, 40.2, 60.2, 60.5, 60.6, 60.6, 63.7, 64.0, 126.4, 126.5, 126.6, 126.6, 127.3, 127.4, 127.4, 127.4, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 129.4, 129.5, 130.3, 130.8, 131.5, 132.5, 136.82, 136.9, 137.5, 137.6, 142.0, 142.9, 174.8, 175.0; Anal. Calcd for $C_{26}H_{29}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.05; H, 7.09; N, 3.66.

1-Phenyl-4-acetyl-4-methyl-1-hexen-5-one (9b): ^1H NMR δ 1.38 (s, 3H), 2.14 (s, 6H), 2.75 (dd, J = 1.2, 7.6 Hz, 2H), 5.97 (dt, J = 7.6, 15.6 Hz, 1H), 6.44 (dt, J = 1.2, 15.6 Hz, 1H), 7.19-7.36 (m, 5H); $^{13}C\{^1H\}$ NMR δ 18.3, 26.7, 38.1,

66.8, 124.0, 126.2, 127.5, 128.5, 134.0, 136.9, 206.7; Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.22; H, 7.88.

2-Carboethoxy-2-(3-phenyl-2-propenyl)-cyclohexan-1-one (9c): ^{1}H NMR δ 1.21 (t, *J* = 7.1 Hz, 3H), 1.49-1.80 (m, 4H), 1.98-2.04 (m, 1H), 2.44-2.55 (m, 4H), 2.74 (ddd, *J* = 1.2, 6.8, 13.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.17 (ddd, *J* = 7.3, 8.3, 15.9 Hz 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 7.17-7.32 (m, 5H); ^{13}C{^{1}H} NMR δ 14.2, 22.6, 27.5, 36.1, 38.6, 41.2, 61.3, 61.4, 125.2, 126.2, 127.2, 128.5, 133.2, 137.3, 171.6, 207.6; Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.37; H, 7.74.

Method B. A typical procedure is given for the reaction of 3-acetoxy-1,3-diphenyl-1-propene (**2**) and sodium phenylsulfinate (Table 3, entry 3). A Merrifield vessel was charged with sodium phenylsulfinate (123 mg, 0.75 mmol), **1a** (100 mg, 10.00 μmol Pd), and 1.50 mL of water. To the mixture was added **2** (126 mg, 0.50 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 144 mg (86%) of 1,3-diphenyl-3-phenylsulfonyl-1-propene (**3g**): ^{1}H NMR δ 4.84 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.58 (dd, *J* = 8.3, 15.9 Hz 1H), 7.23-7.68 (m, 15H); ^{13}C{^{1}H} NMR δ 75.4, 120.0, 126.8, 128.5, 128.6, 128.7, 128.7, 128.9, 129.3, 129.7, 132.3, 133.6, 135.9, 137.4, 138.2; Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.43. Found: C, 75.47; H, 5.47.

1-Azido-1,3-diphenyl-2-propene (3h): ^{1}H NMR δ 5.20 (d, *J* = 7.3 Hz, 1H), 6.28 (dd, *J* = 7.3, 15.6 Hz, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 7.23-7.41 (m, 10H); ^{13}C{^{1}H} NMR δ 67.2, 126.8, 126.9, 127.1, 128.2, 128.3, 128.7, 128.8, 133.0, 135.9, 138.6; Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.78; H, 5.71; N, 17.56.

Allylic Alkylation of 2 with Ethyl Acetoacetate catalyzed by Palladium-TPPTS complex. To a mixture of **2** (126 mg, 0.50 mmol), di(μ-chloro)bis(η^3-allyl)dipalladium(II) (910 μg, 2.50 μmol), TPPTS (5.68 mg, 10.00 μmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (190 mg, 1.25 mmol) in 1.50 mL of THF was added ethyl acetoacetate (98 mg, 0.75 mmol), and the mixture was stirred at 25 °C for 12 h. The alkylation product was not detected on TLC analysis.

Allylic Alkylation of 2 with Ethyl Acetoacetate catalyzed by Palladium-triphenylphosphine complex. To a mixture of **2** (126 mg, 0.50 mmol), di(μ-chloro)bis(η^3-allyl)dipalladium(II) (910 μg, 2.50 μmol), triphenylphosphine (2.62 mg, 10.0 μmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (190 mg, 1.25 mmol) in 1.50 mL of THF was added ethyl acetoacetate (97.6 mg, 0.75 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced

pressure. The residue was diluted with EtOAc and the organic layer was washed twice with water, and then dried over Na_2SO_4. The solution was concentrated under reduced pressure and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 9.6 mg of **3a** (0.03 mmol).

Recycle Experiment of 1a: A Merrifield vessel was charged with **1a** (331 mg, 38.5 μmol Pd). To the vessel were added 1.50 M of aqueous potassium carbonate solution (5.0 mL), **2** (624 mg, 2.47 mmol), and ethyl acetoacetate (215 mg, 1.65 mmol) and the mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with tetrahydrofuran (2 × 5 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give **3a**. The residual beads were dried under reduced pressure for 30 min and reused for the next reaction.

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Chapter III

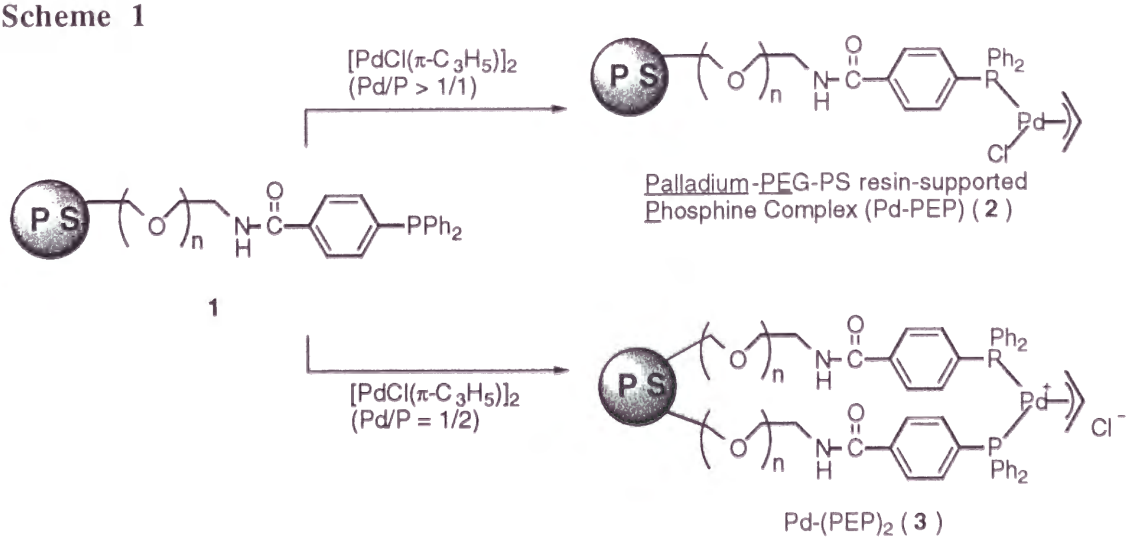
Cross-Coupling of Aryl Halides and Allyl Acetates with Arylboron Reagents in Water Using an Amphiphilic Solid-Supported Palladium Catalyst

Summary: The cross-coupling reaction of aryl halides or allyl acetates with arylboronic acids or sodium tetraphenylborate was catalyzed in water by amphiphilic resin-supported palladium-phosphine complexes bound to a polyethylene glycol-polystyrene graft copolymer (PEG-PS resin). The reaction of aryl halides (PhI, PhBr, 2-$CH_3C_6H_4I$, and 4-$CH_3C_6H_4I$) with arylboron reagents ($PhB(OH)_2$, 4-$CH_3C_6H_4B(OH)_2$, 4-$CH_3OC_6H_4B(OH)_2$, and $NaBPh_4$) in the presence of 2 mol% palladium of Pd-PEP in aqueous alkaline solution at 25 °C gave corresponding biphenyl derivatives in high yields. Pd-PEP also catalyzed allylic arylation of allyl acetates (including 1,3-disubstituted allyl acetates and cyclic allyl acetates) with arylboron reagents in water under the similar reaction conditions to give 80-99% yield of allylarenes.

Introduction

The transition metal-catalyzed cross-coupling of aryl and alkenyl halides with various organometal reagents are useful means of carbon-carbon bond formation. The palladium-catalyzed cross-coupling using organoboron reagents, so-called Suzuki-

Scheme 1

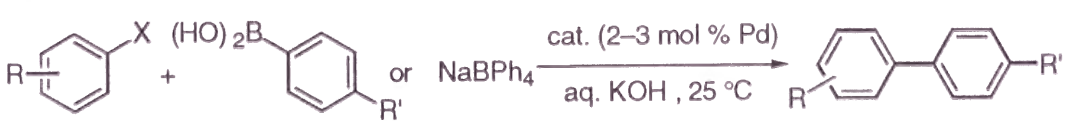


Miyaura coupling is one of the representatives.[1] I have reported design and preparetion of amphiphilic solid-supported triarylphosphine-palladium complex bound to a polyethylene glycol-polystyrene graft copolymer (PEG-PS resin) which exhibit high catalytic activity in allylic substitution reactions of allyl acetates with various nucleophiles in aqueous media under mild reaction conditions.[2]. As a part of our efforts to develop the wide utility of these catalysts, palladium-catalyzed cross-coupling reaction with arylboron reagents was examined in water. I describe herein arylation of aryl halides and allyl acetates with arylboron reagents in aqueous media which is catalyzed by the amphiphilic PEG-PS resin-supported triarylphosphine-palladium complex, Pd-PEP (**2**).[2]

Results and Discussion

Suzuki-Miyaura Coupling. Several palladium-phosphine complexes were examined for the coupling reaction of iodobenzene with phenylboronic acid in water, the Suzuki-Miyaura coupling having been well-documented to take place in aqueous organic media.[1] It was found that solid-supported palladium-phosphine complex catalyzes the coupling reaction to give biphenyl in high yield. The PEG-PS resin-supported palladium complex Pd-PEP (**2**) was readily prepared by treatment of resin-supported phosphine **1**[2] with an exess amount of di(μ-chloro)bis(η3-allyl)dipalladium(II) ($[PdCl(\eta^3\text{-}C_3H_5)]_2$) (P/P > 1/1) followed by removal of unimmobilized $[PdCl(\eta^3\text{-}C_3H_5)]_2$ by washing three times with chloroform (Scheme 1). A mixture of iodobenzene (**4a**) and Phenylboronic acid (**5**) was agitated in water with shaking on a wrist-action shaker in the presence of 4.5 equiv. of potassium hydroxide and 2 mol % of Pd-PEP complex at 25 °C for 24 h. The reaction mixture was filtered and the recovered resin was extracted with chloroform by washing four times. After removal of the solvent, crude mixture was chromatographed on silica gel to give biphenyl **8a** in 88 % yield (Table 1, entry 1). The

Scheme 2



4a (R = H, X = I)
4a' (R = H, X = Br)
4b (R = 2-CH_3, X = I)
4c (R = 4-CH_3, X = I)

5 (R' = H)
6 (R' = CH_3)
7 (R' = OCH_3)

8 a-b (R' = H)
9a-c (R' = CH_3)
1 0a-c (R' = OCH_3)
(**a**: R = H, **b**: R = 2-CH_3, **c**: R = 4-CH_3)

coupling with resin-supported palladium-bis(triarylphosphine) complex **3** (Pd-$(PEP)_2$)[2] gave 80% yield of **8a** (entry 2). The cross-coupling using water-soluble phosphine ligand TPPTS[3,4], showed much lower catalytic activity under the reaction conditions giving 59 % yield of **8a** (entry 3). Palladium-triphenylphosphine complex did not catalyzed the reaction in water owing to its insolubility (entry 4). The arylation with 4-methylphenylboronic acid (**6**) and 4-methoxyphenylboronic acid (**5**) gave bialys **9a** and **10a** in 91 % and 72 % yields, respectively, under the same reaction conditions (entries 5 and 6). The coupling reaction of **4a** with sodium tetraphenylborate took place without

Table 1. Cross-Coupling of Aryl Halides with Arylboron Reagents in Water Catalyzed by Palladium-Phosphine Complexes[a]

entry	aryl halide	arylboron	catalyst	product	yield (%)[b]
1	C_6H_5I (**4a**)	**5**	**2**	**8a**	88
2		**5**	**3**	**8a**	80
3		**5**	Pd/TPPTS[c]	**8a**	59
4		**5**	$Pd(PPh_3)_4$	**6a**	0
5		**6**	**2**	**9a**	91
6		**7**	**2**	**10a**	72
7[d]		$NaBPh_4$	**2**	**8a**	84
8	C_6H_5Br (**4a'**)	**5**	**2**	**8a**	77
9		**6**	**2**	**9a**	82
10		**7**	**2**	**10a**	70
11[d]		$NaBPh_4$	**2**	**8a**	67
12[e]	2-$CH_3C_6H_4I$ (**4b**)	**5**	**2**	**8b**	66
13		**6**	**2**	**9b**	80
14		**7**	**2**	**10b**	72
15[d]		$NaBPh_4$	**2**	**9a**	67
16	4-$CH_3C_6H_4I$ (**4c**)	**5**	**2**	**9a**	85
17		**6**	**2**	**9c**	79
18		**7**	**2**	**10c**	67
19[d]		$NaBPh_4$	**2**	**9a**	70

[a] All reactions were carried out in H_2O with 1.5 equiv of arylboron reagent and 4.5 equiv of KOH in the presence of 2 mol % Pd-phosphine complex at 25 °C for 24 h, unless otherwise noted. [b] Isolated yield. [c] A catalyst generated in situ by mixing $[PdCl(p\text{-}C_3H_5)]_2$ and TPPTS (2 mol % Pd, Pd/P = 1/1) was used. [d] Without KOH. [e] 3 mol % Pd of **2** was used.

base to give 84 % of **8a** (entry 7). Bromobenzene (**4a'**) also underwent the cross-coupling with arylboron reagents at 25 °C by use of Pd-PEP catalyst in water. The reaction of **4a'** with **5**, **6**, and **7** gave biaryls **8a**, **9a**, and **10a** in 77%, 82%, and 70% yield, respectively (entries 8-10). It has been well-documented that Suzuki-Miyaura coupling of aryl halides with arylboronic acids catalyzed by palladium-phosphine complexes requires around 80 °C of the reaction temperature even for aryl iodides.[1] This immobilized Pd-PEP (**2**) shows higher catalytic activity in water than other homogeneous palladium-phosphine complexes so far reported for the present transformation,[1,5] while immobilization of catalysts often causes decrease of catalytic activity in general. The reaction of *o*- and *p*-iodotoluene (**4b** and **4c**) with **5-7** gave the corresponding bialys under the same reaction conditions in 66-85% yield (entries 12-19).

Allylic Arylation. Encouraged by the results obtained in the Suzuki-Miyaura coupling we examined the application of Pd-PEP (**2**) to the allylic arylation using arylboron reagents. Compared to the significant development of the Suzuki-Miyaura coupling, rather surprisingly, only scattered attention has been paid to the use of arylboron reagents for the arylation of allyl alcohol derivatives.[6] In particular, only few works on catalytic allylic arylation of 1,3-disubstituted secondary allyl esters have been reported so far.[7] Recently, Kobayashi et al. have developed nickel-catalyzed arylation of allylic carbonates with lithium organoborates.[8] It was found that Pd-PEP complex **2** catalyzed allylic arylation of secondary as well as primary allyl acetates with arylboronic acid and sodium tetraphenylborate at 25 °C in water (Scheme 2). The results obtained are summarized in Table 2, which also includes those obtained with triphenylphosphine and TPPTS for comparison. A mixture of cinnamyl acetate **11a** (0.5 mmol), phenylboronic acid **3** (1.5 equiv), and potassium carbonate (4.5 equiv) in 1.5 mL of water was shaken in the presence of 2 mol % palladium of Pd-PEP **2** at 25 °C for 24 h to give 99% yield of

Scheme 3

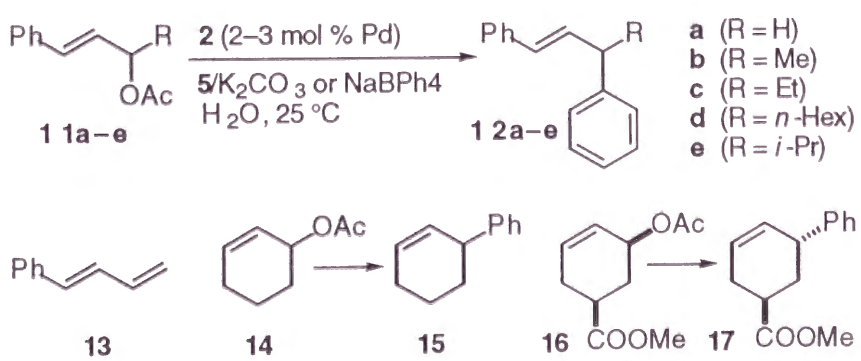


Table 2. Arylation of Allylic Acetates in Water Catalyzed by Pd-PEP (**2**)[a]

entry	allyl acetate	reagent	product	yield (%)[b]
1	**11a**	**5**	**12a**	99
2[c]	**11a**	$NaBPh_4$	**12a**	99
3[d]	**11a**	**5**	**12a**	29
4	**11b**	**5**	**12b**	99
5[e]	**11b**	**5**	**12b**	15
6[f]	**11b**	**5**	**12b**	no reaction
7[g]	**11b**	**5**	**12b**	14[h]
8[c]	**11b**	$NaBPh_4$	**12b**	99
9	**11c**	**5**	**12c**	90
10[c]	**11c**	$NaBPh_4$	**12c**	94
11	**11d**	**5**	**12d**	85
12[c]	**11e**	$NaBPh_4$	**12e**	81[i]
13	**14**	**5**	**15**	90
14	**16**	**5**	**17**	45
15[c]	**16**	$NaBPh_4$	**17**	96

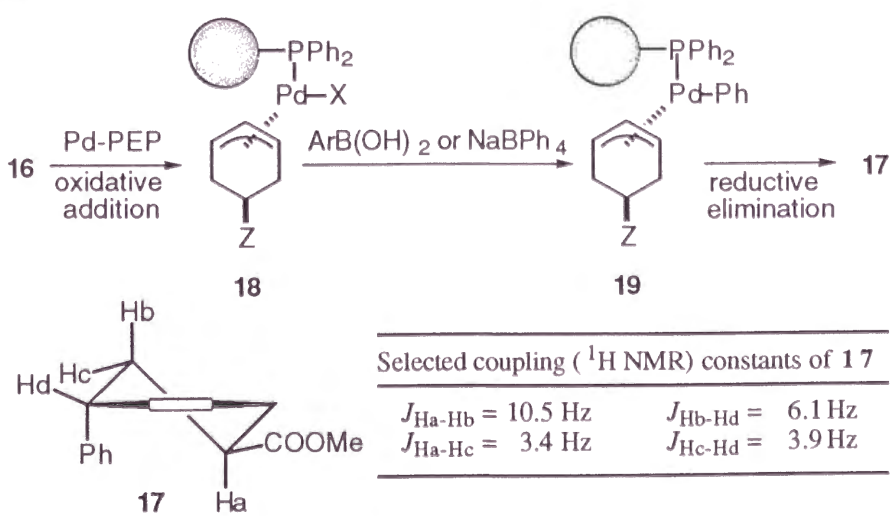
[a] All reactions were carried out with 1.5 equiv of **5** or $NaBPh_4$ in H_2O in the presence of 4.5 equiv of K_2CO_3 and 2 mol % Pd of Pd-PEP (**2**) at 25 °C for 24 h, unless otherwise noted. Allyl acetate (mol)/H_2O (L) = 1.0/3.0. [b] Isolated yield. [c] Without K_2CO_3. [d] Carried out in aqueous benzene solvent (H_2O/benzene = 1.0/5.0). [e] A catalyst generated in situ by mixing $[PdCl(\pi\text{-}C_3H_5)]_2$ and TPPTS (2 mol % Pd, Pd/P = 1/1) was used. [f] 2 mol % of $Pd(PPh_3)_4$ was used at 25 °C in aq. Na_2CO_3/benzene (1.0/5.0). [g] 2 mol % of $Pd(PPh_3)_4$ was used in refluxing aq. Na_2CO_3/benzene (1.0/5.0). [h] 38% yield of 1-phenylbutadiene (**13**) was obtained. [i] 10% yield of regioisomeric product, 1,1-diphenyl-4-methyl-2-pentene, was obtained.

1,3-diphenylpropene (**12a**) (Table 2, entry 1). The solid-supported catalyst was readily recovered by simple filtration and could be taken on to the next series of the reaction. Thus, after completion of the reaction, the solid-supported catalyst was washed twice with THF and water under nitrogen atmosphere in the Merrifield vessel. To the reaction vessel, aqueous potassium carbonate, allyl acetate **11a**, and phenylboronic acid (**5**) were charged and the entire mixture was agitated under the same reaction conditions to give 80% yield of **12a**. The allylic arylation with sodium tetraphenylborate took place in water to give 99% yield of **12a** (entry 2). The Pd-PEP showed much lower catalytic activity in organic reaction media. The allylic arylation of **11a** with **5** in aqueous benzene (H_2O/benzene = 1/5) gave 29% yield of **12a** under otherwise the same reaction

conditions (entry 3). This allylic arylation system using Pd-PEP catalyst, arylboron reagents, and genuine aqueous reaction media was also successfully applied to other substrates which have substituents on their C1 and C3 positions. Thus, reaction of 3-acetoxy-1-phenyl-1-butene (**11b**) with phenylboronic acid (**5**) was catalyzed by 2 mol % palladium of Pd-PEP in water in the presence of potassium carbonate to give 99% yield of 1,3-diphenyl-1-butene (**12b**) as a single regioisomer (entry 4). Palladium-TPPTS complex generated in situ exhibited much lower catalytic activity under the present conditions to give 15% yield of **12b** (entry 5). Tetrakis(triphenylphosphine)palladium did not catalyze the present reaction at 25 °C in aqueous benzene solvent, and the reaction at higher temperature resulted in the formation of conjugated 1,3-diene **13** as a major product (entries 6 and 7). Secondary allylic acetates, 3-acetoxy-1-phenyl-1-pentene (**11c**), 3-acetoxy-1-phenyl-1-nonene (**11d**), and 3-acetoxy-4-methyl-1-phenyl-1-pentene (**11e**) also underwent the alkylation to give **12c**, **12d**, **12e** in 94%, 85%, and 81% yield, respectively (entries 9-12). The Pd-PEP catalyst is also effective for the arylation of 3-acetoxy-1-cyclohexene (**14**) in aqueous potassium carbonate to give 3-phenyl-1-cyclohexene (**15**) in 90% yield (entry 13).

The Pd-PEP catalyzed arylation was found to proceed with inversion of configuration with respect to the stereogenic carbon center where the arylation took place. Thus, the reaction of *cis*-3-acetoxy-5-carbomethoxy-1-cyclohexene (**16**) with phenylboronic acid (**7a**) in the presence of Pd-PEP (2 mol % of Pd) and potassium carbonate in water at 25 °C gave 3-phenyl-5-carbomethoxy-1-cyclohexene (**17**) in 45% yield as a single diastereoisomer (Table 2, entry 14). The chemical yield of arylation was improved by use of sodium tetraphenylborate to 96% without any loss of stereoselectivity (entry 15). The stereochemistry of **17** was assigned to be *trans* by comparison of the ^{1}H NMR

Scheme 4



Selected coupling (^{1}H NMR) constants of **17**	
J_{Ha-Hb} = 10.5 Hz	J_{Hb-Hd} = 6.1 Hz
J_{Ha-Hc} = 3.4 Hz	J_{Hc-Hd} = 3.9 Hz

spectrum with reported data (Scheme 3).[9] This catalytic arylation must proceed via the π-allylpalladium intermediate **18** which formed by the oxidative addition of allylic acetates to a palladium(0) species. The stereochemistry upon oxidative addition to palladium(0) complexes coordinated with phosphine ligands has been reported to be inversion with allylic acetates.[10] It is deduced from the overall inversion of configuration observed here in the catalytic arylation that the stereochemistry upon arylation of π-allylpalladium is retention, indicating that the aryl group attacks the palladium atom of the π-allylpalladium intermediate to form the π-allyl(aryl)palladium intermediate **19** and reductive elimination gives the allylarene **17**. The inversion of configuration at catalytic allylic arylation has been also observed in the nickel-catalyzed arylation of allylic carbonates with lithium arylborate.[8a]

Experimental Section

General. All manipulations were carried out under nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JMN-EX270 spectrometer (270 MHz for ^1H), JEOL JMN-LA400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C), or JEOL JMN-LA500 spectrometer (500 MHz for ^1H). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. The agitation of the reaction mixture was performed on a wrist-action shaker (Burrel Scientific, Inc.).

Materials. THF was dried over sodium benzophenone ketyl and distilled prior to use. Dichloromethane was dried over calcium hydride and distilled prior to use. Water was distilled prior to use. Pd-PEP catalyst (**2,3**) was prepared on commercially available polystyrene-polyethylene graft copolymer beads, TentaGel S-NH_2 (Rapp Polymere, Germany) according to the procedure reported in chapter I. Phenylboronic acid (**5**), 4-methylphenylboronic acid (**6**), and 4-methoxyphenylboronic acid (**7**) were purchased from Aldrich Chemical Co. Inc. Sodium tetraphenylborate was purchased from Wako Chemical Co. Inc.

General Procedure for the Cross-Coupling. Method A: Reaction of Aryl Halides with Arylboronic Acids. A Merrifield vessel was charged with aryl halide (0.50 mmol), arylboronic acid (0.75 mmol), 1.50 M of potassium hydroxide aqueous solution (1.5 mL), and **2** (100 mg, 10.0 μmol Pd), and the mixture was shaken on a wrist-action shaker at 25 °C for 24 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4

and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: pentane) to give coupling product.

Method B: Reaction of Aryl Halides with Sodium Tetraphenylborate. A Merrifield vessel was charged with aryl halide (0.50 mmol), sodium tetraphenylborate (257 mg, 0.75 mmol), 1.5 mL of water and **2** (100 mg, 10.0 μmol Pd), and the mixture was shaken on a wrist-action shaker at 25 °C for 24 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: pentane) to give coupling product.

Biphenyl (**8a**), 2-methylbiphenyl (**8b**), 4-methylbiphenyl (**9a**), 2,4'-dimethylbiphenyl (**9b**), and 4,4'-dimethylbiphenyl (**9c**) 4-methoxybiphenyl (**10a**), 4-methoxy-2'-methylbiphenyl (**10b**), and 4-methoxy-4'-methylbiphenyl (**10c**) are known compounds.[11]

Preparation of Allyl Acetates (11b-e). A typical procedure is given for the preparation of **3-acetoxy-1-phenyl-1-butene (11b).**[11,12] To a solution of cinnamaldehyde (2.64 g, 20 mmol) in 30 mL of tetrahydrofuran was added a 0.87 M tetrahydrofuran solution of methylmagnesium bromide (34.0 mL, 30.0 mmol) at 0 °C. After being stirred for 2 h, the mixture was diluted with 30 mL of ether and quenched with a small amount of saturated NH_4Cl. The resulting suspension was filtered through Celite and the filter cake was washed 3 times with ether. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc = 3/1) to give 1-phenyl-1-buten-3-ol. To a dichloromethane (20.0 mL) solution of 1-phenyl-1-buten-3-ol was added pyridine (5.0 mL) and acetic anhydride (5.0 mL) at 0 °C and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether. The organic layer was washed with water and saturated $CuSO_4$, and dried over Na_2SO_4. After removal of solvent, chromatography on silica gel (hexane/EtOAc = 10/1) followed by Kugelrohr distillation (pot temperature 135 °C/4 mmHg) gave 2.96 g (78% for 2 steps) of 3-acetoxy-1-phenyl-1-butene (**11b**) as a colorless oil: ^{1}H NMR δ 1.25 (d, J = 6.6 Hz, 3H), 2.07 (s, 3H), 5.53 (quintet, J = 6.6 Hz, 1H), 6.18 (dd, J = 6.6, 16.1 Hz, 1H), 6.60 (d, J = 16.1 Hz, 1H), 7.23-7.39 (m, 5H).

3-Acetoxy-1-phenyl-1-pentene (11c):[11] ^{1}H NMR δ 0.94 (t, J = 7.6 Hz, 3H), 1.73 (dq, J = 6.9, 7.6 Hz, 2H), 2.08 (s, 3H), 5.34 (dt, J = 6.9, 7.3 Hz, 1H), 6.12 (dd, J = 7.3, 16.2 Hz, 1H), 6.60 (d, J = 16.2 Hz, 1H), 7.24-7.40 (m, 5H).

3-Acetoxy-1-phenyl-1-nonene (11d): ^{1}H NMR δ 0.88 (t, J = 6.8 Hz, 3H), 1.25-1.33 (m, 8H), 1.61-1.76 (m, 2H), 2.07 (s, 3H), 5.39 (dt, J = 6.6, 7.1 Hz, 1H), 6.12 (dd, J = 7.3, 16.1 Hz, 1H), 6.60 (d, J = 16.1 Hz, 1H), 7.22-7.39 (m, 5H); ^{13}C{^{1}H} NMR δ 14.1, 21.3, 22.6, 25.2, 29.1, 31.7, 34.6, 74.8, 126.6, 127.87,

127.90, 128.6, 132.4, 136.5, 170.3; Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.14; H, 9.09.

3-Acetoxy-4-methyl-1-phenyl-1-butene (11e):[11] ^{1}H NMR δ 0.95 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.96 (octet, *J* = 6.6 Hz, 1H), 2.09 (s, 3H), 5.21 (dd, *J* = 6.6, 7.6 Hz, 1H), 6.12 (dd, *J* = 7.6, 15.8 Hz, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 7.24-7.41 (m, 5H). .

3-Acetoxy-1,3-diphenyl-1-propene (11f):[11] ^{1}H NMR δ 2.14 (s, 3H), 6.35 (dd, *J* = 7.3, 15.8 Hz, 1H), 6.44 (d, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 7.23-7.42 (m, 10H).

3-Acetoxy-1-cyclohexene (**14**)[11] and 3-acetoxy-5-methoxycarbonyl-1-cyclohexene (**16**)[13] were prepared according to the reported procedures.

General Procedure for the Allylic Arylation. Method A: Reaction of Allyl Acetates with Arylboronic Acids. A Merrifield vessel was charged with arylboronic acid (0.75 mmol), potassium carbonate (311 mg, 2.25 mmol), **2** (100 mg, 10.0 μmol Pd), and 1.5 mL of water. To a mixture was added allyl acetate (0.50 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 24 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: pentane) to give arylation product.

Method B: Reaction of Aryl Halides with Sodium Tetraphenylborate. A Merrifield vessel was charged with sodium tetraphenylborate (257 mg, 0.75 mmol), **1** (100 mg, 10.0 μmol Pd), and 1.5 mL of water. To a mixture was added allyl acetate (0.50 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 24 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: pentane) to give arylation product.

1,3-Diphenylpropene (**12a**),[6b] 1,3-diphenyl-1-butene (**12b**),[12] 1,3,3-triphenyl-1-propene (**12f**),[11] 1-phenyl-1,3-butadiene (**13**),[11] 3-phenyl-1-cyclohexene (**15**),[17] and 5-methoxycarbonyl-3-phenyl-1-cyclohexene (**17**)[8a] are known compounds.

1,3-Diphenyl-1-pentene (12c): ^{1}H NMR δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.78-1.1.89 (m, 2H), 3.31 (quintet, *J* = 7.3 Hz, 1H), 6.33 (dd, *J* = 7.3, 15.8 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 7.16-7.35 (m, 10H); $^{13}C\{^1H\}$ NMR δ 12.3, 28.8, 51.0, 126.1, 126.2, 127.0, 127.7, 128.5, 129.5, 134.2, 137.6, 144.5; Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.54; H, 8.46.

1,3-Diphenyl-1-nonene (12d): ^{1}H NMR δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.24-1.37 (m, 8H), 1.79 (dt, *J* = 6.8, 7.3 Hz, 2H), 3.40 (dt, *J* = 7.3,7.3 Hz, 1H), 6.32 (dd, *J* = 7.3, 15.8 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 7.16-7.35 (m, 10H); $^{13}C\{^1H\}$ NMR

δ 14.1, 22.7, 27.6, 29.3, 31.8, 35.9, 49.2, 126.1, 126.2, 127.0, 127.6, 128.4, 128.5, 129.3, 134.5, 137.7, 144.8; Anal. Calcd for $C_{21}H_{26}$: C, 90.59; H, 9.41. Found: C, 90.57; H, 9.36.

4-Methyl-1,3-diphenyl-1-pentene (12e): ^{1}H NMR δ 0.71 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 2.00-2.09 (m, 1H), 3.02-3.07 (m, 1H), 6.38-6.39 (m, 2H), 7.17-7.35 (m, 10H); ^{13}C{^{1}H} NMR δ 20.9, 21.2, 33.2, 57.6, 126.0, 126.1, 127.0, 128.0, 128.4, 128.4, 130.3, 133.2, 137.7, 144.3; Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.23; H, 8.61.

5-Methoxycarbonyl-3-phenyl-1-cyclohexene (17): ^{1}H NMR δ 1.97 (ddd, *J* = 3.4, 3.9, 13.2 Hz, 1H), 2.16 (ddd, *J* = 6.1, 10.5, 13.2 Hz, 1H), 2.33-2.37 (m, 2H), 2.58-2.65 (m, 1H), 3.54-3.60 (m, 1H), 5.76-5.80 (m, 1H), 5.93-5.98 (m, 1H), 7.20-7.33 (m, 5H).

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[113334-98-8]; **11e** [108814-27-3]; **12a** [3412-44-0]; **12b** [7302-01-4]; **12c** [189322-54-1]; **12d** [203316-75-0]; **13** [16939-57-4]; **14** [76704-31-9]; **15** [15232-96-9]; **16** [11518-98-1], [60729-55-7]; **17** [82342-65-2].

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Chapter IV

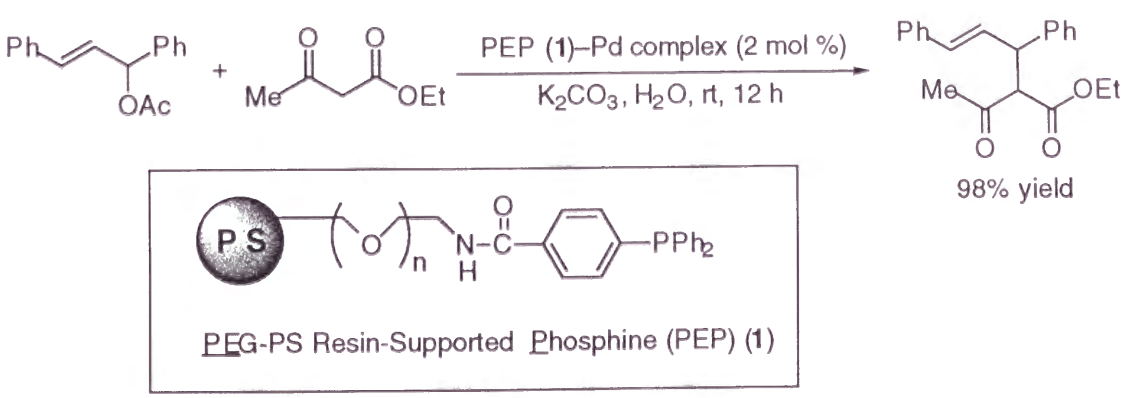
Palladium-Catalyzed Asymmetric Allylic Substitution in Aqueous Media Using Amphiphilic Solid-Supported MOP Ligands

Summary: A series of amphiphilic resin-supported MOP ligands PEP-MOP were prepared on a polyethylene glycol-polystyrene graft copolymer. Palladium complexes of PEP-MOP were found to be effective as catalysts for the asymmetric substitution of 1,3-diphenyl-2-acetoxypropene with 3-methyl-2,4-pentanedione in aqueous potassium carbonate to give 4-acetyl-1,3-diphenyl-4-methyl-1-hexen-5-one of up to 81% ee.

Introduction

I have previously reported design and preparation of amphiphilic palladium-phosphine complexes bound to PEG-PS resin which exhibit high catalytic activity in allylic substitution reactions of allyl acetates with various nucleophiles in aqueous media under mild reaction conditions (Scheme 1).[1] On the other hand, it had been reported that 2-diarylphosphino-1,1'-binaphthyls MOP[2] prepared by Uozumi and Hayashi exhibit high asymmetric induction ability in the palladium-catalyzed reactions,[3] such as hydrosilylation of olefins[3a] or reduction of allyl esters with formic acid.[4] Providing that MOP ligand is immobilized on solid-supports, the palladium-catalyzed asymmetric reactions can take place in aqueous media.

Scheme 1

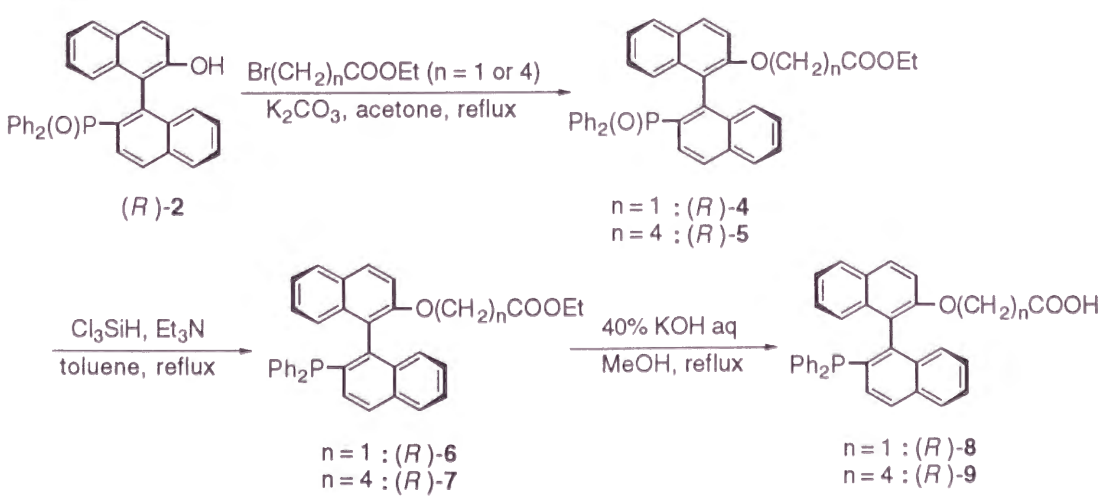


In this chapter I prepared the MOP ligands bound to amphiphilic resin supports and the catalytic activity and asymmetric induction ability in aqueous media was examined in the palladium-catalyzed asymmetric allylic substitution.[5] Various amino acids were incorporated between a supported MOP ligand and a terminal amino residue of PEG-PS resin as diversity elements. These ligands with various structures were applied for the reaction of 1,3-diphenyl-2-acetoxypropene with 3-methyl-2,4-pentanedione.[6]

Results and Discussion

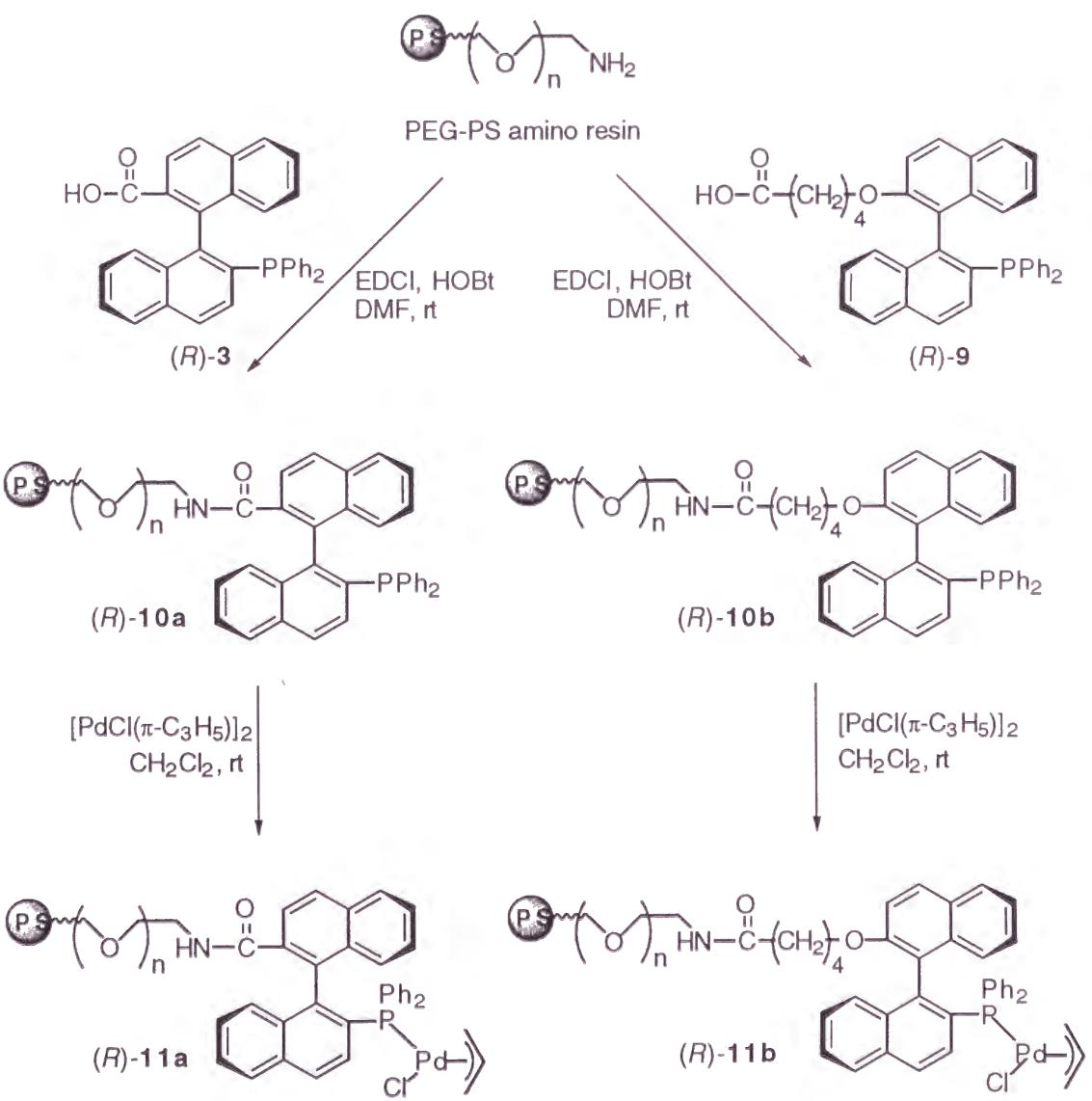
It was reported in the previous chapter that the resin-supported phosphine (PEP, **1**) was readily prepared by dehydrative condensation of diphenylphosphinobenzoic acid with terminal amino residue of PEG chain on the polystyrene matrix. According to this protocol, various types of ligands bearing carboxylic group should be immobilized on the PEG-PS resin. It has been well-documented that various functional groups are readily introduced at the 2' position of chiral binaphthyl backbone of MOP.[2] A carboxylic group was introduced at the 2' position of MOP skeleton to serve as the site for attachment to the solid support. The phenolic hydroxy group of (*R*)-2-(diphenylphosphinyl)-2'-hydroxybinaphthyl ((*R*)-**2**) was alkylated by treatment with ethyl 2-bromoacetate and ethyl 5-bromovalerate in the presence of potassium carbonate to give ethyl (*R*)-2-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)acetate (*R*)-**4** (98% yield) and ethyl (*R*)-5-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)pentanoate (*R*)-**5** (88% yield), respectively (Scheme 2). Reduction of phosphine oxide (*R*)-**4** and (*R*)-**5** with trichlorosilane and triethylamine[7] in toluene upon heating gave phosphines (*R*)-**6** and (*R*)-**7** in 77% and 86% yield, respectively. Hydrolysis of the ethyl ester group of (*R*)-**6** and (*R*)-**7** with aqueous

Scheme 2



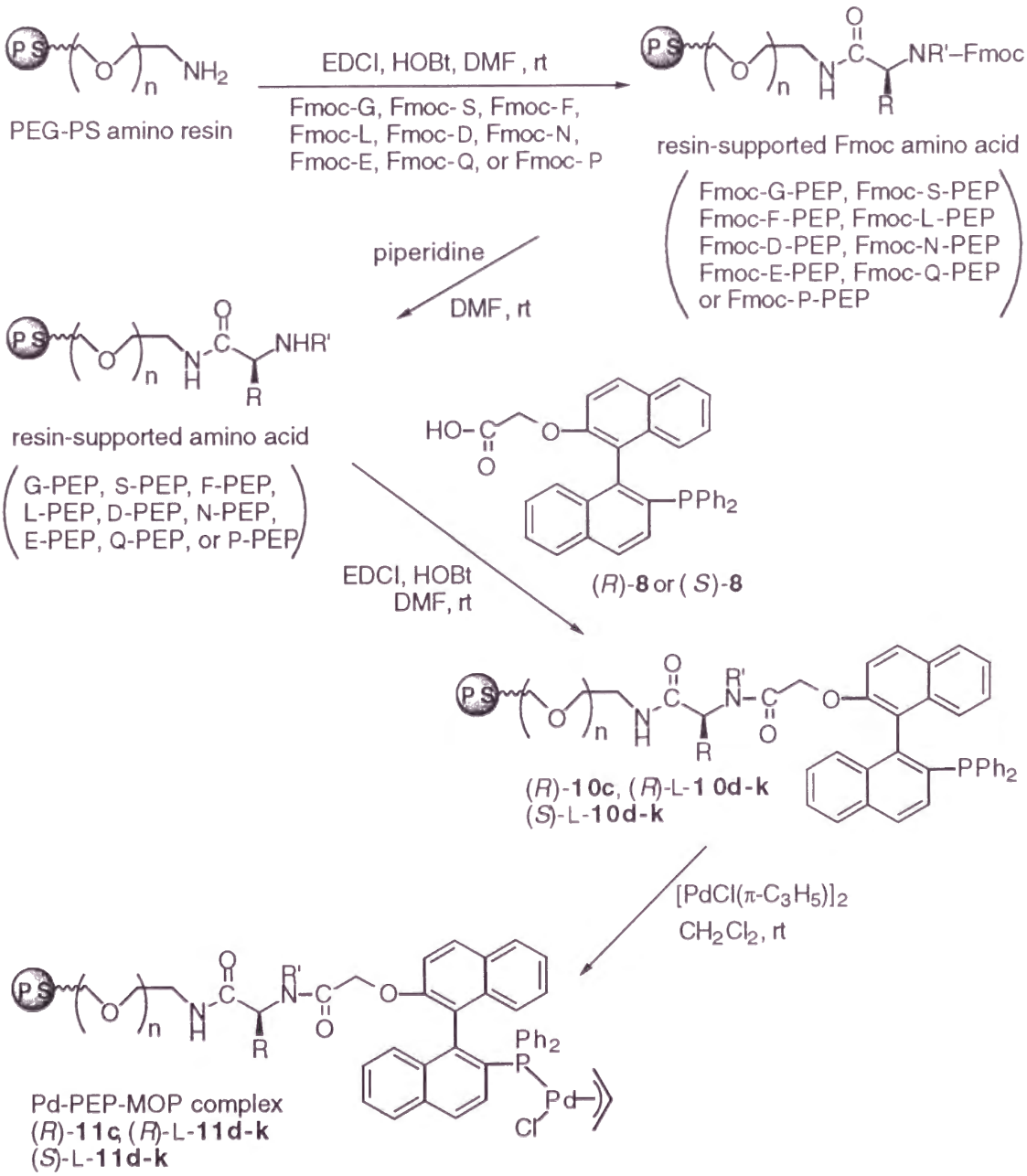
potassium hydroxide in methanol gave (*R*)-2-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)acetic acid (*R*)-**8** and (*R*)-5-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)pentanoic acid (*R*)-**9** in 100% and 78% yield, respectively. The enantiomeric isomer (*S*)-**8** was prepared by the same method starting with (*S*)-**2**. Amphiphilic resin-supported MOP ligands PEP-MOP (PEG-PS resin-supported MOP) **10a** and **10b** were readily prepared on a polyethylene glycol-polystyrene graft copolymer having amino group (PEG-PS amino resin) from (*R*)-2-diphenylphosphino-1,1'-binaphthyl-2'-carboxylic acid ((*R*)-**3**)[2b] and (*R*)-**9**, respectively, in a similar manner to the procedure reported in chapter 1 (Scheme 3). Thus, a mixture of PEG-PS amino resin, 2 equiv of (*R*)-**3** or (*R*)-**9**, 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (EDCI•HCl) (3 equiv), and 1-

Scheme 3



hydroxybenzotriazole (HOBt) (4 equiv) was agitated in DMF at ambient temperature on a wrist-action shaker until a negative Kaiser test indicating the completion of the reaction to form (*R*)-PEP-MOP (*R*)-**10a** or (*R*)-**10b**, quantitatively. According to the same procedure, a library of PEP-MOP ligands containing α-amino acid unit in their tether regions was prepared from resin-bound aminoacids (Scheme 4).[8] Thus, Fmoc amino acids (Fmoc-G, Fmoc-S, Fmoc-F, Fmoc-L, Fmoc-D, Fmoc-N, Fmoc-E, Fmoc-Q, and Fmoc-P)[9] were condensed with terminal amino group of PEG-PS amino resin in the

Scheme 4



presence of EDCI•HCl and HOBt in DMF to give corresponding resin-bound Fmoc amino acids. The Fmoc group was removed by treatment with piperidine in DMF to give resin-bound amino acids (G-PEP, S-PEP, F-PEP, L-PEP, D-PEP, N-PEP, E-PEP, Q-PEP, and P-PEP).[9] MOP derivative (*R*) or (*S*)-**8**, EDCI•HCl, HOBt, and DMF were added to resin-bound amino acids and agitated at ambient temperature. After negative Kaiser test was observed, the beads were rinsed with DMF and dichloromethane, and dried under reduced pressure to give resin-bound MOP (**10c-10k**). Treatment of PEP-MOP **10a-k** with di(μ-chloro)bis(η^3-allyl)palladium(II) in dichloromethane at ambient temperature for 10 min gave corresponding resin-supported palladium-phosphine complexes **11a-k**. Analysis of **11** for contents of palladium and phosphorus by ICP-atomic emission spectroscopy showed the ratio of Pd/P was 1/1.

Asymmetric catalysis in water was realized in the palladium-catalyzed allylic substitution by use of the amphiphilic resin-supported chiral palladium-phosphine complex **11** prepared above. Thus, asymmetric substitution of 1,3-diphenyl-2-propenyl acetate (**12**) with 3-methyl-2,4-pentanedione (**13**) in an aqueous solution of potassium carbonate was carried out at 25 °C for 12 h in the presence of 2 mol % palladium of the catalyst resin **11** to give optically active 1,3-diphenyl-4-acetyl-4-methyl-1-hexen-5-one (**14**) (Scheme 5). The substituted product **14** was isolated by silica gel column chromatography and the enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Chiralcel OD-H, eluent: hexane/2-propanol = 98/2). The absolute configuration of **14** was determined by comparison of its retention time of the HPLC analysis with an authentic sample prepared from (*R*)-1,3-diphenyl-4-acetyl-1-hexen-5-one.[10] It was found that the catalytic activity and the enantioselectivity of palladium-PEP-MOP complexes are affected by their tether unit. Thus, the allylic substitution with palladium complex (*R*)-**11b** which has 5-oxypentanoyl tether gave 55% ee of (*R*)-**14** in 56% yield, while (*R*)-**11a** gave <5% yield of (*R*)-**14** with much lower enantioselectivity (14% ee) (Table 1, entries 1 and 2). The use of a palladium complex (*R*)-**11c**, in which MOP moiety is located seven atoms away from the PEG region as is in (*R*)-**11b**, showed almost the same catalytic activity as (*R*)-**11b** to give 58% yield of

Scheme 5

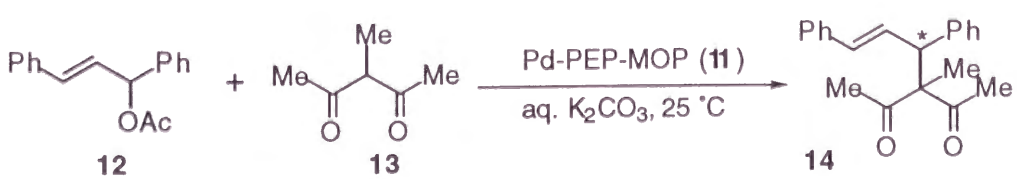


Table 1. Asymmetric Substitution of **12** with **13** in Aqueous Potassium Carbonate Catalyzed by Palladium-PEP-MOP Complexes[a]

entry	catalyst	yield (%)[b] of **14**	% ee[c] (abs. config.)
1	(*R*)-**11a**	<5	14 (*R*)
2	(*R*)-**11b**	56	55 (*R*)
3	(*R*)-**11c**	58	74 (*R*)
4	(*R*)-L-**11d**	68	81 (*R*)[d]
5	(*R*)-L-**11e**	75	81 (*R*)
6	(*R*)-L-**11f**	75	81 (*R*)
7[e]	(*R*)-L-**11f**	45	84 (*R*)
8[f]	(*R*)-L-**11f**	58	77 (*R*)
9[g]	(*R*)-L-**11f**	62	77 (*R*)
10	(*R*)-L-**11g**	58	81 (*R*)
11	(*R*)-L-**11h**	50	75 (*R*)
12	(*R*)-L-**11i**	74	78 (*R*)
13	(*R*)-L-**11j**	54	78 (*R*)
14	(*R*)-L-**11k**	71	61 (*R*)
15	(*S*)-L-**11d**	52	77 (*S*)
16	(*S*)-L-**11e**	49	78 (*S*)
17	(*S*)-L-**11f**	49	78 (*S*)
18	(*S*)-L-**11g**	54	83 (*S*)
19	(*S*)-L-**11h**	61	76 (*S*)
20	(*S*)-L-**11i**	75	75 (*S*)
21	(*S*)-L-**11j**	65	73 (*S*)
22	(*S*)-L-**11k**	42	62 (*S*)

[a] The reaction was carried out in aqueous potassium carbonate in the presence of 2 mol % palladium of a Pd-PEP-MOP complex **11** at 25 °C for 12 h with agitation on a wrist-action shaker. The ratio of **12** (mol)/**13** (mol)/base (mol)/H_2O (L) = 1.0/1.5/4.5/3.0. [b] Isolated yield by silica gel column chromatography. [c] Determined by HPLC analysis with chiral stationary phase column (Chiralcel OD-H, eluent: hexane/isopropanol = 98/2). d $[\alpha]_D^{24}$ –22 (*c* 1.7, ethanol). [e] Lithium carbonate was used as base. [f] Sodium carbonate was used as base. [g] Cesium carbonate was used as base.

14, and the enantioselectivity was increased to 74% ee (*R*) under the same reaction conditions (entry 3). Among the palladium-PEP-MOP complexes (*R*)-L-**11d-k**, and (*S*)-L-**11d-k**, which contain L-Ser(*t*-Bu), L-Phe, L-Leu, L-Asp(O*t*-Bu), L-Asn, L-Glu(O*t*-

Bu), L-Gln, and L-Pro groups in their tether regions, (*R*)-L-**11d**, (*R*)-L-**11e**, and (*R*)-L-**11f** were found to be effective chiral catalysts for the present allylic substitution (entries 4,5, and 6). They gave (*R*)-**14** of 81% ee. Effect of inorganic bases of the enantioselectivity and/or catalytic activity has been examined using this catalyst system. Of lithium, sodium, potassium, and cesium carbonates, potassium carbonate gave the best result (entries 6-9). Lithium carbonate gave lower chemical yield (45%) of **14**, though the enantioselectivity was 84% ee. Comparing a pair of diastereomeric palladium-PEP-MOP complexes (*R*)-L-**11f** and (*S*)-L-**11f**, both of which contain the L-Leu group in their tether regions, the catalytic activity of (*R*)-L-**11f** is higher than that of (*S*)-L-**11f** and the stereochemical outcome is determined mainly by the configuration of MOP moiety (entries 6 and 17). The allylic alkylation of **12** with the sodium salt of **13** in THF in the presence of palladium-(*R*)-MeO-MOP complex (2 mol %) gave <5% yield of (*R*)-**14** (57% ee) at 25 °C for 12h.

Experimental Section

General. All manipulations were carried out under nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, SICAPENT). NMR spectra were recorded on a JEOL JMN-EX270 spectrometer (270 MHz for ^1H and 109 MHz for ^{31}P), JEOL JMN-AL400 spectrometer (400 MHz for ^1H), JEOL JMN-LA400 spectrometer (400 MHz for ^1H), or JEOL JMN-LA500 spectrometer (500 MHz for ^1H and 202 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR, and to an external 85% H_3PO_4 standard for ^{31}P NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. ^1H, ^{13}C, ^{31}P, NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. HPLC analysis was performed on a Shimadzu LC 6A liquid chromatograph system and a JASCO PU-980 liquid chromatograph system with chiral stationary phase column DAICEL CHIRALCEL OD-H. Optical rotations were measured on a JASCO DIP-1000 polarimeter. The agitation of the reaction mixture was performed on a wrist-action shaker (Burrel Scientific, Inc.).

Materials. THF was dried over sodium benzophenone ketyl and distilled prior to use. DMF and dichloromethane was dried over calcium hydride and distilled prior to use. Water was distilled prior to use. TentaGel S-NH_2 was purchased from Rapp Polymere (Germany). 3-Methyl-2,4-pentanedione (**13**) were purchased from Aldrich Chemical Co. Inc. 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI•HCl) and 1-hydroxybenzotriazole (HOBt) were purchased from Nacalai Tesque Co. Inc. 9-Fluorenylmethoxycarbonyl amino acids (Fmoc amino acids) were purchased from Wako Chemical Co. Inc. (*R*)-(–)-2-(Diphenylphosphinyl)-2'-hydroxybinaphthyl ((*R*)-**2**)[2a],

(*R*)-(+)-2'-diphenylphosphino-1,1'-binaphthyl-2-carboxylic acid ((*R*)-**3**)[2b], and 1,3-diphenyl-2-propenylacetate (**12**) were prepared according to the reported procedures. 4-Acetyl-4-methyl-1,3-diphenyl-1-hexen-5-one (**14**) was reported in chapter I.

Ethyl (*R*)-(+)-2-(2-diphenylphosphinyl-1,1'-binaphthyl-2'-oxy)acetate ((*R*)-4). To a mixture of (*R*)-2-(diphenylphosphinyl)-2'-hydroxy-1,1'-binaphthyl ((*R*)-**2**) (470 mg, 1.00 mmol) and potassium carbonate (691 mg, 5.00 mmol) in acetone (7.00 mL) was added ethyl bromoacetate (835 mg, 5.00 mmol) at ambient temperature, and the reaction mixture was refluxed for 12 h. After being cooled to room temperature, the mixture was filtered through Celite, and the filter cake was washed 3 times with ether. The combined organic layer was concentrated under reduced pressure and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 1/1) to give 544 mg (98%) of (*R*)-**4** as a white solid: $[\alpha]^{22}_{D}$ +115 (*c* 2.0, chloroform); ^{1}H NMR δ 1.13 (t, *J* = 7.4 Hz, 3H), 4.10 (m, 2H), 4.43 (d, *J* = 16.7 Hz, 1H), 4.48 (d, *J* = 16.7 Hz, 1H), 6.77-7.99 (m, 22H); ^{31}P{^{1}H} NMR δ 30.0 (s). Anal. Calcd for $C_{36}H_{29}O_4P$: C, 77.69; H, 5.25. Found: C, 77.56; H, 5.25.

Ethyl (*R*)-(+)-5-(2-diphenylphosphinyl-1,1'-binaphthyl-2'-oxy)pentanoate ((*R*)-5). To a mixture of (*R*)-2-(diphenylphosphinyl)-2'-hydroxy-1,1'-binaphthyl ((*R*)-**2**) (470 mg, 1.00 mmol) and potassium carbonate (691 mg, 5.00 mmol) in acetone (7.00 mL) was added ethyl 5-bromovalerate (1050 mg, 5.00 mmol) at ambient temperature, and the reaction mixture was refluxed for 12 h. After being cooled to room temperature, the mixture was filtered through Celite, and the filter cake was washed 3 times with ether. The combined organic layer was concentrated under reduced pressure and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 1/1) to give 524 mg (88%) of (*R*)-**5** as a white solid: $[\alpha]^{25}_{D}$ +122 (*c* 2.0, chloroform); ^{1}H NMR δ 1.17-1.29 (m, 5H), 1.41-1.52 (m, 2H), 1.92 (t, *J* = 7.6 Hz, 2H), 3.77 (m, 1H), 3.90 (m, 1H), 4.04 (q, *J* = 7.3 Hz, 2H), 6.86-8.00 (m, 22H); ^{31}P{^{1}H} NMR δ 29.2 (s).

Ethyl (*R*)-(+)-2-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)acetate ((*R*)-6). To a mixture of (*R*)-**4** (556 mg, 1.00 mmol) and triethylamine (4.05 g, 40.0 mmol) in toluene (30.0 mL) was added trichlorosilane (1.35 g, 10.0 mmol) at 0 °C and The reaction mixture was refluxed for 8 h. After being cooled to room temperature, the mixture was diluted with 10 mL of ether and quenched with small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite, and the filter cake was washed 3 times with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc, 10/1) to give 416 mg (77%) of (*R*)-**6**: $[\alpha]^{25}_{D}$ +74 (*c* 2.0, chloroform); ^{1}H NMR δ 1.10 (t, *J* = 7.1 Hz, 3H), 4.01 (d, *J* = 16.6 Hz, 1H), 4.01-4.10 (m, 2H), 4.23 (d, *J* = 16.6 Hz, 1H), 6.92-7.96 (m, 22H);

$^{31}P\{^1H\}$ NMR δ –10.5 (s). Anal. Calcd for $C_{36}H_{29}O_3P$: C, 79.98; H, 5.41. Found: C, 79.68; H, 5.37.

Ethyl (*R*)-(+)-5-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)pentanoate ((*R*)-7). To a mixture of (*R*)-**5** (230 mg, 384 μmol) and triethylamine (1.55 g, 15.4 mmol) in toluene (10.0 mL) was added trichlorosilane (520 mg, 3.84 mmol) at 0 °C and the reaction mixture was refluxed for 8 h. After being cooled to room temperature, the mixture was diluted with 10 mL of ether and quenched with small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite, and the filter cake was washed 3 times with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc, 10/1) to give 188 mg (84%) of (*R*)-**7**: $[\alpha]^{26}_D$ +53 (*c* 2.0, chloroform); ^1H NMR δ 1.16-1.31 (m, 7H), 1.86 (t, *J* = 7.3 Hz, 2H), 3.70-3.79 (m, 2H), 4.03 (q, *J* = 7.3 Hz, 2H), 6.90-7.98 (m, 22H); $^{31}P\{^1H\}$ NMR δ –12.8 (s). Anal. Calcd for $C_{39}H_{35}O_3P$: C, 80.39; H, 6.05. Found: C, 80.28; H, 6.04.

(*R*)-(+)-2-(2-Diphenylphosphino-1,1'-binaphthyl-2'-oxy)acetic acid ((*R*)-8). To a solution of (*R*)-**6** (416 mg, 0.77 mmol) in methanol (8.50 mL) was added 1.70 mL of 40% aqueous potassium hydroxide solution at ambient temperature and the reaction mixture was refluxed for 12 h. After being cooled to room temperature, the mixture was acidified (pH = 2) by addition of conc. HCl, and then extracted twice with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: EtOAc) to give (*R*)-**8** (394 mg, 100%): $[\alpha]^{26}_D$ +31 (*c* 2.0, chloroform); ^1H NMR δ 4.29 (d, *J* = 16.2 Hz, 1H), 4.47 (d, *J* = 16.2 Hz, 1H), 6.77-7.99 (m, 22H); $^{31}P\{^1H\}$ NMR δ –11.4 (s).

(*R*)-(+)-5-(2-Diphenylphosphino-1,1'-binaphthyl-2'-oxy)pentanoic acid ((*R*)-9). To a solution of (*R*)-**7** (140 mg, 0.24 mmol) in methanol (3.40 mL) was added 0.70 mL of 40% aqueous potassium hydroxide solution at ambient temperature and the reaction mixture was refluxed for 9 h. After being cooled to room temperature, the mixture was acidified (pH = 2) by addition of conc. HCl, and then extracted twice with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: EtOAc) to give (*R*)-**9** (104 mg, 78%): $[\alpha]^{26}_D$ +50 (*c* 2.0, chloroform); ^1H NMR δ 1.19-1.33 (m, 4H), 1.87 (t, *J* = 7.3 Hz, 2H), 3.70-3.81 (m, 2H), 6.91-7.97 (m, 22H); $^{31}P\{^1H\}$ NMR δ –12.9 (s). Anal. Calcd for $C_{37}H_{31}O_3P$: C, 80.13; H, 5.63. Found: C, 79.86; H, 5.74.

Preparation of Solid-Supported MOP Ligand. Typical procedures were given for the preparation of (*R*)-**10a**. A Merrifield vessel was charged with TentaGel S-NH_2 (200 mg, 123 μmol/g), (*R*)-**3** (31.8 mg, 66.0 μmol), EDCI•HCl (16.9 mg, 88.0 μmol), HOBt (14.9 mg, 0.11 mmol), and DMF (4.0 mL) and the mixture was shaken on a wrist-action shaker at 25 °C for 4 h. The reaction mixture was filtered and the resin was

washed with DMF (5 × 4 mL) and dichloromethane (8 × 4 mL). The resin was dried under reduced pressure to give (*R*)-**10a**: $^{31}P\{^{1}H\}$ NMR δ –14.9 (s).

(*R*)-10b: $^{31}P\{^{1}H\}$ NMR δ –12.9 (s).

Preparation of Solid-Supported MOP Ligand Containing α-Amino Acid Unit (10c-k). A mixture of PEG-PS amino resin (200 mg, 0.123 mmol/g), Fmoc-amino acid (0.050 mmol), EDCI•HCl (28.8 mg, 0.15 mmol), and HOBt (20.4 mg, 0.15 mmol) in 4.00 mL of DMF was shaken at 25 °C for 3 h and then filtered and washed with DMF (5 × 4 mL). The resin was treated with 20% piperidine in DMF (3 × 5 mL) and then washed with DMF (5 × 4 mL). To the resin was added the solution of (*R*) or (*S*)-**8** (25.6 mg, 50.0 μmol), EDCI•HCl (14.4 mg, 75.0 μmol), and HOBt (10.2 mg, 75.0 μmol) in DMF (4.0 mL) and the mixture was shaken at 25 °C for 9 h. After filtration, the resin beads were washed with DMF (5 × 4 mL) and dichloromethane (8 × 4 mL) and dried under reduced pressure to give (*R*) or (*S*)-**10c-k**.

Preparation of Solid-Supported MOP-Palladium Complex (11a-k). A typical procedure was given for the preparation of (*R*)-**11a**. A mixture of (*R*)-**10a** (211 mg, 0.123 mmol/g) and di(μ-chloro)bis(η^3-allyl)dipalladium(II) (4.39 mg, 12.0 μmol) in 4.0 mL of dichloromethane was shaken at 25 °C for 10 min and then filtered and washed with dichloromethane (5 × 4 mL). The resin was dried under reduced pressure to give (*R*)-**11a**: $^{31}P\{^{1}H\}$ NMR δ 15.0 (s), 15.8 (s).

(*R*)-11b: $^{31}P\{^{1}H\}$ NMR δ 14.5 (s), 17.5 (s).

Allylic Substitution of 1,3-Diphenyl-2-propenylacetate (12) with 3-Methyl-2,4-pentanedione (13) Catalyzed by the Solid-Supported Complexes 11a-k. A Merrifield vessel was charged with potassium carbonate (311 mg, 2.25 mmol), solid-supported complex **11a-k** (10.0 μmol Pd) and 1.50 mL of water. To a mixture was added **12** (126 mg, 0.50 mmol) and **13** (85.6 mg, 0.75 mmol) at ambient temperature and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with chloroform (4 × 6 mL). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give 4-acetyl-4-methyl-1,3-diphenyl-1-hexen-5-one (**14**).

Determination of Absolute Configuration and Enantiomeric Purity of 14: The absolute configurations of **14** given in Table 1 were determined by comparison of its retention time of the HPLC analysis with an authentic sample prepared from 4-acetyl-1,3-diphenyl-1-hexen-5-one (82% ee (*R*)) by methylation with methyl iodide and tetrabutylammonium fluoride. Experimental procedures: 4-acetyl-1,3-diphenyl-1-hexen-5-one (58.5 mg, 0.20 mmol) and tetrabutylammonium fluoride (63.1 mg, 0.20 mmol) were dissolved in 10.0 mL of chloroform and stirred for 10 min. The solution was concentrated under reduced pressure and the residue was dissolved in 20.0 mL of chloroform. To the solution was added methyl iodide (142 mg, 1.00 mmol) at ambient

temperature and the reaction mixture was stirred for 24 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel (eluent: hexane/EtOAc = 10/1) to give (*R*)-**14** (82% ee). The conditions for the determination of the enantiomeric purities of **14** with chiral stationary phase columns: DAICEL CHIRALCEL OD-H; hexane/2-propanol = 98/2; *R* isomer eluted faster than *S* isomer.

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List of Publications

Chapter I and II	Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 3557–3560.
Chapter III	Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* submitted
Chapter IV	Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303–8306.